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(54) Title
AMINO ACID DERIVATES

(57) Claim

1. Amino acid derivatives of the formula I

$$X\text{-}Z\text{-}NR^2\text{-}CHR^3\text{-}CHOH\text{-}(CH_2)_n\text{-}NR^4\text{-}E\text{-}Y \quad I$$

in which

X is H, $R^1\text{-}O\text{-}C_mH_{2m}\text{-}CO\text{-}$, $R^1\text{-}C_mH_{2m}\text{-}O\text{-}CO\text{-}$, $R^1\text{-}C_mH_{2m}\text{-}CO\text{-}$, $R^1\text{-}SO_2\text{-}$ or $(R^1\text{-}C_mH_{2m})\text{-}L(R^1\text{-}C_pH_{2p})\text{-}C_rH_{2r}\text{-}CO\text{-}$,

Z is 1 to 4 amino acid radicals bonded to one another in a peptide fashion and selected from the group comprising Abu, Ada, Ala, Arg, Asn, Asp, Bia, Cal, Dab, Gln, Glu, Gly, His, Hph, N(im)-alkyl-His, Ile, Leu, tert.-Leu, Lys, Met, αNal, βNal, Nbg, Nle, Orn, Phe, Pro, Pyr, Ser, Thr, Tic, Trp, Tyr and Val,

E is -CONH-, -CSNH-, -COO-, $-SO_2-$, $-SO_2NH-$ or -PO(OA)-O-,

Y is R^5, $-(CHR^5)_s-COOR^6$ or $-(CHR^5)_s-CONR^7R^8$,

R^1, R^3, R^6, R^7 and R^8 are in each case H, A, Ar, Ar-alkyl, Het, Het-alkyl, or cycloalkyl having 3-7 carbon atoms, cycloalkylalkyl having 4-11 carbon atoms, bicycloalkyl or tricycloalkyl in each case having 7-14 carbon atoms or bicycloalkylalkyl or tricycloalkylalkyl in each case having 8-18 carbon atoms which is in each case unsubstituted or monosubstituted or polysubstituted by A, AO and/or Hal,

R^2 and R^4 are in each case H or A,

R^5 is H, A, Ar, Ar-alkyl, cycloalkyl having 3-7 carbon atoms or cycloalkylalkyl having 4-11 carbon atoms,

L is CH or N,

m, p and r are in each case 0, 1, 2, 3, 4 or 5,

n is 1 or 2,

s is 0 or 1,

Ar is phenyl which is unsubstituted or monosubstituted or polysubstituted by A, AO, Hal, CF_3, OH and/or NH_2, or is unsubstituted naphthyl,

Het is a saturated or unsaturated 5- or 6-membered heterocyclic radical having 1-4 N, O and/or S atoms which may be fused to a benzene ring and/or may be monosubstituted or polysubstituted by A, AO, Hal, CF_3, HO, O_2N, carbonyl oxygen, H_2N, HAN,

A_2N, AcNH, AS, ASO, ASO_2, AOOC, CN, H_2NCO, H_2NSO_2, ASO_2NH, Ar, Ar-alkenyl, hydroxyalkyl and/or aminoalkyl in each case having 1-8 carbon atoms and/or whose N and/or S hetero atoms may also be oxidized,

Hal is F, Cl, Br or I,

Ac is A-CO-, Ar-CO- or A-NH-CO-,

-alkyl- is an alkylene group having 1-8 carbon atoms and

A is alkyl having 1-8 carbon atoms, and

E-Y may also be pyrrolidinocarbonyl, piperidinocarbonyl, morpholinocarbonyl, pyrrolidinosulfonyl, piperidinosulfonyl or morpholinosulfonyl,

and in which, furthermore, one or more -NH-CO groups can be replaced by one or more -NA-CO groups,

and the salts thereof.

6. Use of compounds of the formula I or of their physiologically acceptable salts for combating renin-dependent hypertension or hyperaldosteronism.

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COMPLETE SPECIFICATION

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Complete Specification for the invention entitled AMINO ACID DERIVATES.

The following statement is a full description of this invention including the best method of performing it known to me:-

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ASC 49

Merck Patent Gesellschaft
mit beschrankter Haftung
6100 D a r m s t a d t

Amino acid derivatives

The invention relates to novel amino acid derivatives of the formula I

$$X\text{-}Z\text{-}NR^2\text{-}CHR^3\text{-}CHOH\text{-}(CH_2)_n\text{-}NR^4\text{-}E\text{-}Y \qquad I$$

in which

X is H, $R^1\text{-}O\text{-}C_mH_{2m}\text{-}CO\text{-}$, $R^1\text{-}C_mH_{2m}\text{-}O\text{-}CO\text{-}$, $R^1\text{-}C_mH_{2m}\text{-}CO\text{-}$, $R^1\text{-}SO_2\text{-}$ or $(R^1\text{-}C_mH_{2m})\text{-}L(R^1\text{-}C_pH_{2p})\text{-}C_rH_{2r}\text{-}CO\text{-}$,

Z is 1 to 4 amino acid radicals bonded to one another in a peptide fashion and selected from the group comprising Abu, Ada, Ala, Arg, Asn, Asp, Bia, Cal, Dab, Gln, Glu, Gly, His, Hph, N(im)-alkyl-His, Ile, Leu, tert.-Leu, Lys, Met, αNal, βNal, Nbg, Nle, Orn, Phe, Pro, Pyr, Ser, Thr, Tic, Trp, Tyr and Val,

E is -CONH-, -CSNH-, -COO-, $-SO_2-$, $-SO_2NH-$ or -PO(OA)-O-,

Y is R^5, $-(CHR^5)_s\text{-}COOR^6$ or $-(CHR^5)_s\text{-}CONR^7R^8$,

R^1, R^3, R^6, R^7 and R^8 are in each case H, A, Ar, Ar-alkyl, Het, Het-alkyl, or cycloalkyl having 3-7 carbon atoms, cycloalkylalkyl having 4-11 carbon atoms, bicycloalkyl or tricycloalkyl in each case having 7-14 carbon atoms or bicycloalkylalkyl or

tricycloalkylalkyl in each case having 8-18 carbon atoms which is in each case unsubstituted or monosubstituted or polysubstituted by A, AO and/or Hal,

R^2 and R^4 are in each case H or A,

R^5 is H, A, Ar, Ar-alkyl, cycloalkyl having 3-7 carbon atoms or cycloalkylalkyl having 4-11 carbon atoms,

L is CH or N,

m, p and r are in each case 0, 1, 2, 3, 4 or 5,

n is 1 or 2,

s is 0 or 1,

Ar is phenyl which is unsubstituted or monosubstituted or polysubstituted by A, AO, Hal, CF_3, OH and/or NH_2, or is unsubstituted naphthyl,

Het is a saturated or unsaturated 5- or 6-membered heterocyclic radical having 1-4 N, O and/or S atoms which may be fused to a benzene ring and/or may be monosubstituted or polysubstituted by A, AO, Hal, CF_3, HO, O_2N, carbonyl oxygen, H_2N, HAN, A_2N, AcNH, AS, ASO, ASO_2, AOOC, CN, H_2NCO, H_2NSO_2, ASO_2NH, Ar, Ar-alkenyl, hydroxyalkyl and/or aminoalkyl in each case having 1-8 carbon atoms and/or whose N and/or S hetero atoms may also be oxidized,

Hal is F, Cl, Br or I,

Ac	is A-CO-, Ar-CO- or A-NH-CO-,
-alkyl-	is an alkylene group having 1-8 carbon atoms and
A	is alkyl having 1-8 carbon atoms, and
E-Y	may also be pyrrolidinocarbonyl, piperidinocarbonyl, morpholinocarbonyl, pyrrolidinosulfonyl, piperidinosulfonyl or morpholinosulfonyl,

and in which, furthermore, one or more -NH-CO groups can be replaced by one or more -NA-CO groups,

and the salts thereof.

Similar compounds have been disclosed by EP-A-77,028, EP-A-155,809, EP-A-156,321, EP-A-156,322 and EP-A-163,237, but in particular by US-A-4,599,198.

The invention had the object of finding new compounds having valuable properties, in particular those which can be used for the preparation of medicaments.

It has been found that the compounds of the formula I, and their salts, have very valuable properties. Above all, they inhibit the activity of human plasma renin. This action can be detected, for example, using the method of F. Fyhrquist et al., Clin. Chem. 22, 250-256 (1976). It is notable that these compounds are very specific inhibitors of renin; for the inhibition of other aspartyl-proteinases (for example pepsin and kathepsin D), significantly higher concentrations of these compounds are generally necessary.

The compounds can be employed as active ingredients in medicaments in human and veterinary medicine, in particular

for prophylaxis and treatment of coronary, circulatory and vascular disorders, above all hypertonia, cardiac insufficiency and hyperaldosteronism. In addition, the compounds can be used for diagnostic purposes in order to determine the possible contribution of renin activity to maintenance of the pathological state in patients having hypertonia or hyperaldosteronism.

The above- and belowmentioned abbreviations of amino acid radicals represent the radicals -NH-CHR-CO- (in which R has the specific meaning known for each amino acid) of the following amino acids:

Abu	2-aminobutyric acid
Ada	adamantylalanine
Ala	alanine
Arg	arginine
Asn	asparagine
Asp	aspartic acid
Bia	benzimidazolylalanine
Cal	cyclohexylalanine
Dab	2,4-diaminobutyric acid
Gln	glutamine
Glu	glutamic acid
Gly	glycine
His	histidine
N(im)-alkyl-His	histidine which is substituted in the 1-position of the imidazole ring by A
Hph	homo-phenylalanine (2-amino-4-phenylbutyric acid)
Ile	isoleucine
Leu	leucine
tert.-Leu	tert.-leucine
Lys	lysine
Met	methionine
αNal	α-naphthylalanine
βNal	β-naphthylalanine
Nbg	(2-norbornyl)-glycine

Nle	norleucine
N-Me-His	N-methyl-histidine
N-Me-Phe	N-methyl-phenylalanine
Orn	ornithine
Phe	phenylalanine
Pro	proline
Pyr	pyridylalanine
Ser	serine
Thr	threonine
Tic	tetrahydroisoquinoline-1-carboxylic acid
Trp	tryptophan
Tyr	tyrosine
Val	valine.

Furthermore, the following terms have the following meanings:

BOC	tert.-butoxycarbonyl
imi-BOM	benzyloxymethyl in the 1-position of the imidazole ring
CBZ	benzyloxycarbonyl
DNP	2,4-dinitrophenyl
imi-DNP	2,4-dinitrophenyl in the 1-position of the imidazole ring
ETNC	N-ethylcarbamoyl
ETOC	ethoxycarbonyl
FMOC	9-fluorenylmethoxycarbonyl
IPNC	N-isopropylcarbamoyl
IPOC	isopropoxycarbonyl
MC	morpholinocarbonyl
OMe	methyl ester
OEt	ethyl ester
PBB	4-phenyl-2-benzylbutyryl
POA	phenoxyacetyl
DCCI	dicyclohexylcarbodiimide
HOBt	1-hydroxybenzotriazole.

In cases where it is possible for the abovementioned amino

acids to occur in several enantiomeric forms, all these forms and also mixtures thereof (for example the DL forms) are included above and below, for example as part of the compounds of the formula I. The L forms are preferred. Where individual compounds are listed below, the abbreviations for these amino acids in each case relate to the L form, unless expressly stated otherwise.

The radicals or parameters X, Z, E, Y, D, R^1 to R^9, L, m, n, p, r, Ar, Het, Hal, Ac, -alkyl-, A, G^1, G^2, Z^1 and Z^2 above and below have the meanings specified in the formula I, II or III, unless expressly stated otherwise. If two radicals R^1 are present in a compound of the formula I, they may be identical or different from one another.

In the formulae above, A has 1-8, preferably 1, 2, 3 or 4 carbon atoms. A is preferably methyl, furthermore ethyl, propyl, isopropyl, butyl, isobutyl, sec.-butyl or tert.-butyl, furthermore also pentyl, 1-, 2- or 3-methylbutyl, 1,1-, 1,2- or 2,2-dimethylpropyl, 1-ethylpropyl, hexyl, 1-, 2-, 3- or 4-methylpentyl, 1,1-, 1,2-, 1,3-, 2,2-, 2,3- or 3,3-dimethylbutyl, 1- or 2-ethylbutyl, 1-ethyl-1-methylpropyl, 1-ethyl-2-methylpropyl, 1,1,2- or 1,2,2-trimethylpropyl, heptyl or octyl.

Cycloalkyl is preferably cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl, but alterratively, for example, 1-, 2- or 3-methylcyclopentyl, or 1-, 2-, 3- or 4-methylcyclohexyl.

Accordingly, cycloalkyl-alkyl is preferably cyclopropylmethyl, 2-cyclopropylethyl, cyclobutylmethyl, 2-cyclobutylethyl, cyclopentylmethyl, 2-cyclopentylethyl, cyclohexylmethyl, 2-cyclohexylethyl, but alternatively, for example, 1-, 2- or 3-methylcyclopentylmethyl, or 1-, 2-, 3- or 4-methylcyclohexylmethyl.

Bicycloalkyl is preferably 1- or 2-decalyl, 2-bicyclo-

[2,2,1]heptyl or 6,6-dimethyl-2-bicyclo[3,1,1]heptyl.

Tricycloalkyl is preferably 2-adamantyl.

Hal is preferably F, Cl or Br, but alternatively I.

Ac is preferably A-CO-, such as acetyl, propionyl or butyryl, Ar-CO-, such as benzoyl, o-, m- or p-methoxybenzoyl or 3,4-dimethoxybenzoyl, or A-NH-CO-, such as N-methyl- or N-ethylcarbamoyl.

Ar is preferably phenyl, furthermore preferably o-, m- or p-tolyl, o-, m- or p-ethylphenyl, o-, m- or p-methoxyphenyl, o-, m- or p-fluorophenyl, o-, m- or p-chlorophenyl, o-, m- or p-bromophenyl, o-, m- or p-iodophenyl, o-, m- or p-trifluoromethylphenyl, o-, m- or p-hydroxyphenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or 3,5-dimethoxyphenyl, 3,4,5-trimethoxyphenyl, o-, m- or p-aminophenyl, or 1- or 2-naphthyl.

Accordingly, Ar-alkyl is preferably benzyl, 1- or 2-phenylethyl, o-, m- or p-methylbenzyl, 1- or 2-o-, -m- or -p-tolylethyl, o-, m- or p-ethylbenzyl, 1- or 2-o-, -m- or -p-ethylphenylethyl, o-, m- or p-methoxybenzyl, 1- or 2-o-, -m- or -p-methoxyphenylethyl, o-, m- or p-fluorobenzyl, 1- or 2-o-, -m- or -p-fluorophenylethyl, o-, m- or p-chlorobenzyl, 1- or 2-o-, -m- or -p-chlorophenylethyl, o-, m- or p-bromobenzyl, 1- or 2-o-, -m- or -p-bromophenylethyl, o-, m- or p-iodobenzyl, 1- or 2-o-, -m- or -p-iodophenylethyl, o-, m- or p-trifluoromethylbenzyl, o-, m- or p-hydroxybenzyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or 3,5-dimethoxybenzyl, 3,4,5-trimethoxybenzyl, o-, m- or p-aminobenzyl, or 1- or 2-naphthylmethyl.

Het is preferably 2- or 3-furyl, 2- or 3-thienyl, 1-, 2- or 3-pyrryl, 1-, 2-, 4- or 5-imidazolyl, 1-, 3-, 4- or 5-pyrazolyl, 2-, 4- or 5-oxazolyl, 3-, 4- or 5-isoxazolyl, 2-, 4- or 5-thiazolyl, 3-, 4- or 5-isothiazolyl, 2-, 3-

or 4-pyridyl, 2-, 4-, 5- or 6-pyrimidyl, furthermore preferably 1,2,3-triazol-1-, -4- or -5-yl, 1,2,4-triazol-1-, -3- or -5-yl, 1- or 5-tetrazolyl, 1,2,3-oxadiazol-4- or -5-yl, 1,2,4-oxadiazol-3- or -5-yl, 1,3,4-thiadiazol-2- or -5-yl, 1,2,4-thiadiazol-3- or -5-yl, 2,1,5-thiadiazol-3- or -4-yl, 2-, 3-, 4-, 5- or 6-2H-thiopyranyl, 2-, 3- or 4-4H-thiopyranyl, 3- or 4-pyridazinyl, pyrazinyl, 2-, 3-, 4-, 5-, 6- or 7-benzofuryl, 2-, 3-, 4-, 5-, 6- or 7-benzothienyl, 1-, 2-, 3-, 4-, 5-, 6- or 7-indolyl, 1-, 2-, 3-, 4-, 5-, 6- or 7-isoindolyl, 1-, 2-, 4- or 5-benzimidazolyl, 1-, 3-, 4-, 5-, 6- or 7-benzopyrazolyl, 2-, 4-, 5-, 6- or 7-benzoxazolyl, 3-, 4-, 5-, 6- or 7-benzisoxazolyl, 2-, 4-, 5-, 6- or 7-benzothiazolyl, 2-, 4-, 5-, 6- or 7-benzisothiazolyl, 4-, 5-, 6- or 7-benz-2,1,3-oxadiazolyl, 2-, 3-, 4-, 5-, 6-, 7- or 8-quinolyl, 1-, 3-, 4-, 5-, 6-, 7- or 8-isoquinolyl, 1-, 2-, 3-, 4- or 9-carbazolyl, 1-, 2-, 3-, 4-, 5-, 6-, 7-, 8- or 9-acridinyl, 3-, 4-, 5-, 6-, 7- or 8-cinnolyl, or 2-, 4-, 5-, 6-, 7- or 8-quinazolyl. The heterocyclic radicals may also be partly or completely hydrogenated. Het can thus also be, for example, 2,3-dihydro-2-, -3-, -4- or -5-furyl, 2,5-dihydro-2-, -3-, -4- or -5-furyl, tetrahydro-2- or -3-furyl, tetrahydro-2- or -3-thienyl, 2,3-dihydro-1-, -2-, -3-, -4- or -5-pyrryl, 2,5-dihydro-1-, -2-, -3-, -4- or -5-pyrryl, 1-, 2- or 3-pyrrolidinyl, tetrahydro-1-, -2- or -4-imidazolyl, 2,3-dihydro-1-, -2-, -3-, -4- or -5-pyrazolyl, 2,5-dihydro-1-, -2-, -3-, -4- or -5-pyrazolyl, tetrahydro-1-, -3- or -4-pyrazolyl, 1,4-dihydro-1-, -2-, -3- or -4-pyridyl, 1,2,3,4-tetrahydro-1-, -2-, -3-, -4-, -5- or -6-pyridyl, 1,2,3,6-tetrahydro-1-, -2-, -3-, -4-, -5- or -6-pyridyl, 1-, 2-, 3- or 4-piperidinyl, 2-, 3- or 4-morpholinyl, tetrahydro-2-, -3- or -4-pyranyl, 1,4-dioxanyl, 1,3-dioxan-2-, -4- or -5-yl, hexahydro-1-, -3- or -4-pyridazinyl, hexahydro-1-, -2-, -4- or -5-pyrimidyl, 1-, 2- or 3-piperazinyl, 1,2,3,4-tetrahydro-1-, -2-, -3-, -4-, -5-, -6-, -7- or -8-quinolyl, or 1,2,3,4-tetrahydro-1-, -2-, -3-, -4-, -5-, -6-, -7- or -8-isoquinolyl.

The heterocyclic radicals may also be substituted as specified. Het may thus preferably also be: 2-amino-4-thiazolyl, 4-carboxy-2-thiazolyl, 4-carbamoyl-2-thiazolyl, 4-(2-aminoethyl)-2-thiazolyl, 2-amino-5,6-dimethyl-3-pyrazinyl, 4-carbamoylpiperidino, furthermore, for example, 3-, 4- or 5-methyl-2-furyl, 2-, 4- or 5-methyl-3-furyl, 2,4-dimethyl-3-furyl, 5-nitro-2-furyl, 5-styryl-2-furyl, 3-, 4- or 5-methyl-2-thienyl, 2-, 4- or 5-methyl-3-thienyl, 3-methyl-5-tert.-butyl-2-thienyl, 5-chloro-2-thienyl, 5-phenyl-2- or -3-thienyl, 1-, 3-, 4- or 5-methyl-2-pyrryl, 1-methyl-4- or -5-nitro-2-pyrryl, 3,5-dimethyl-4-ethyl-2-pyrryl, 4-methyl-5-pyrazolyl, 4- or 5-methyl-2-thiazolyl, 2- or 5-methyl-4-thiazolyl, 2- or 4-methyl-5-thiazolyl, 2,4-dimethyl-5-thiazolyl, 3-, 4-, 5- or 6-methyl-2-pyridyl, 2-, 4-, 5- or 6-methyl-3-pyridyl, 2- or 3-methyl-4-pyridyl, 3-, 4-, 5- or 6-chloro-2-pyridyl, 2-, 4-, 5- or 6-chloro-3-pyridyl, 2- or 3-chloro-4-pyridyl, 2,6-dichloropyridyl, 2-hydroxy-3-, -4-, -5- or -6-pyridyl (= 1H-2-pyridon-3-, -4-, -5- or -6-yl), 5-phenyl-1H-2-pyridon-3-yl, 5-p-methoxyphenyl-1H-2-pyridon-3-yl, 2-methyl-3-hydroxy-4-hydroxymethyl-5-pyridyl, 2-hydroxy-4-amino-6-methyl-3-pyridyl, 3-N'-methylureido-1H-4-pyridon-5-yl, 5- or 6-methyl-4-pyrimidyl, 2,6-dihydroxy-4-pyrimidyl, 5-chloro-2-methyl-4-pyrimidyl, 2-methyl-4-amino-5-pyrimidyl, 3-methyl-2-benzofuryl, 2-ethyl-3-benzofuryl, 7-methyl-2-benzothienyl, 1-, 2-, 4-, 5-, 6- or 7-methyl-3-indolyl, 1-methyl-5- or -6-benzimidazolyl, 1-ethyl-5- or -6-benzimidazolyl, or 3-, 4-, 5-, 6-, 7- or 8-hydroxy-2-quinolyl.

R^1 is preferably A, in particular methyl, ethyl, propyl, isopropyl, butyl, isobutyl or tert.-butyl, furthermore preferably cyclopropyl, cyclopentyl, cyclohexyl, phenyl, benzyl or morpholino.

R^2 and R^4 are preferably H or methyl, furthermore ethyl, propyl, isopropyl, butyl or isobutyl.

R^3 is preferably cyclohexylmethyl, furthermore preferably A, in particular methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec.-butyl, pentyl, isopentyl (3-methylbutyl) or 2-methylbutyl, phenyl, benzyl, p-chlorobenzyl, 2-cyclohexylethyl, bicyclo[2,2,1]heptyl-2-methyl or 6,6-dimethylbicyclo[3,1,1]heptyl-2-methyl.

R^5 is preferably H; A, in particular methyl, ethyl, isopropyl, isobutyl, sec.-butyl or isopentyl; Ar, in particular phenyl; or cycloalkyl, in particular cyclohexyl.

R^6 is preferably A, in particular methyl, ethyl, propyl, isopropyl, butyl, isobutyl or sec.-butyl.

R^7 is preferably H, methyl, ethyl, isobutyl or sec.-butyl, furthermore preferably propyl, butyl, cyclohexyl, cyclohexylmethyl, phenyl or benzyl, in addition preferably Het-alkyl, in particular Het-methyl or 2-Het-ethyl, individually preferably 5-tetrazolylmethyl, 2-, 3- or 4-pyridylmethyl, 2-(2-, 2-(3- or 2-(4-pyridyl)-ethyl, 2-hydroxy-4,6-dimethyl-3-pyridylmethyl, 2-methyl-4-amino-5-pyrimidylmethyl or 2-amino-5,6-dimethyl-3-pyrazinylmethyl.

R^8 is preferably H, furthermore methyl, ethyl or phenyl.

L is preferably CH.

m, p and r are preferably 0, 1 or 2; n is preferably 1; s is preferably 1.

X is preferably H, POA, alkoxycarbonyl, such as ETOC, IPOC or BOC, CBZ, alkanoyl, such as acetyl, propionyl, butyryl or isobutyryl, cycloalkylcarbonyl, such as cyclopentylcarbonyl or cyclohexylcarbonyl, aroyl, such as benzoyl, arylalkanoyl, such as phenylacetyl, 2- or 3-phenylpropionyl, 4-phenylbutyryl, 2-benzyl-3-phenylpropionyl, PBB, 2-(2-phenylethyl)-4-phenylbutyryl, 2-(1-

naphthylmethyl)-4-phenylbutyryl, 2- or 3-o-, -m- or -p-fluorophenylpropionyl, 2- or 3-o-, -m- or -p-chlorophenylpropionyl, cycloalkylalkanoyl, such as cyclohexylacetyl, 2- or 3-cyclohexylpropionyl, N-alkylcarbamoyl, such as ETNC or IPNC, or MC. Particularly preferred radicals X are BOC and MC, furthermore ETOC, IPOC, ETNC, IPNC and PBB, furthermore H, POA, 4-phenylbutyryl, 2-benzyl-3-phenylpropionyl, 2-(2-phenylethyl)-4-phenylbutyryl, 2-(1-naphthylmethyl)-4-phenylbutyryl and CBZ.

Z is preferably 2, but alternatively 1, furthermore 3 or 4 amino acid radicals bonded to one another in a peptide fashion, in particular one of the groups His, Phe-His or Phe-Gly, furthermore preferably the groups Abu, Ada, Asn, Bia, Cal, Gln, N-(im)-methyl-His, Leu, αNal, βNal, Nle, Phe, Trp, Tyr, Abu-His, Ada-His, Ala-His, Ala-Phe, Arg-His, Asn-His, Bia-His, Cal-His, Dab-His, Glu-His, His-His, Hph-His, Ile-His, Leu-His, tert.-Leu-His, Lys-His, Met-His, αNal-His, βNal-His, Nbg-His, Nle-His, (N-Me-His)-His, (N-Me-Phe)-His, Orn-His, Phe-Abu, Phe-Ada, Phe-Ala, Phe-Arg, Phe-Asn, Phe-Bia, Phe-Cal, Phe-Dab, Phe-Gln, Phe-Glu, Phe-(N-im-methyl-His), Phe-Ile, Phe-Leu, Phe-tert.-Leu, Phe-Lys, Phe-Met, Phe-αNal, Phe-βNal, Phe-Nbg, Phe-Nle, Phe-(N-Me-His), Phe-(N-Me-Phe), Phe-Orn, Phe-Phe, Phe-Pro, Phe-(2-Pyr), Phe-(3-Pyr), Phe-(4-Pyr), Phe-Ser, Phe-Thr, Phe-Tic, Phe-Trp, Phe-Tyr, Phe-Val, Pro-His, Ser-His, Thr-His, Tic-His, Trp-His, Tyr-His, Val-His, furthermore Ada-Phe-His, Pro-Ala-His, Pro-Ala-Phe, Pro-Phe-Ala, Pro-Phe-His, Pro-Phe-Phe, His-Pro-Ala-His, His-Pro-Ala-Phe, His-Pro-Phe-Ala, His-Pro-Phe-Phe, furthermore Pro-Abu-His, Pro-Ada-His, Pro-Arg-His, Pro-Asn-His, Pro-Bia-His, Pro-Dab-His, Pro-Glu-His, Pro-His-His, Pro-Ile-His, Pro-Leu-His, Pro-tert.-Leu-His, Pro-Lys-His, Pro-Met-His, Pro-Nbg-His, Pro-Nle-His, Pro-(N-Me-His)-His, Pro-(N-Me-Phe)-His, Pro-Orn-His, Pro-Phe-Abu, Pro-Phe-Ada, Pro-Phe-Arg, Pro-Phe-Asn, Pro-Phe-Bia, Pro-Phe-Dab, Pro-Phe-Gln, Pro-Phe-Glu, Pro-Phe-(N-im-methyl-His), Pro-Phe-Ile, Pro-Phe-Leu, Pro-Phe-tert.-Leu,

Pro-Phe-Lys, Pro-Phe-Met, Pro-Phe-Nbg, Pro-Phe-Nle, Pro-Phe-(N-Me-His), Pro-Phe-(N-Me-Phe), Pro-Phe-Orn, Pro-Phe-Pro, Pro-Phe-Ser, Pro-Phe-Thr, Pro-Phe-Tic, Pro-Phe-Trp, Pro-Phe-Tyr, Pro-Phe-Val, Pro-Pro-His, Pro-Ser-His, Pro-Thr-His, Pro-Tic-His, Pro-Trp-His, Pro-Tyr-His, Pro-Val-His, His-Pro-Abu-His, His-Pro-Ada-His, His-Pro-Arg-His, His-Pro-Asn-His, His-Pro-Bia-His, His-Pro-Dab-His, His-Pro-Glu-His, His-Pro-His-His, His-Pro-Ile-His, His-Pro-Leu-His, His-Pro-tert.-Leu-His, His-Pro-Lys-His, His-Pro-Met-His, His-Pro-Nbg-His, His-Pro-Nle-His, His-Pro-(N-Me-His)-His, His-Pro-(N-Me-Phe)-His, His-Pro-Orn-His, His-Pro-Phe-Abu, His-Pro-Phe-Ada, His-Pro-Phe-Arg, His-Pro-Phe-Asn, His-Pro-Phe-Bia, His-Pro-Phe-Dab, His-Pro-Phe-Gln, His-Pro-Phe-Glu, His-Pro-Phe-His, His-Pro-Phe(N-im-methyl-His), His-Pro-Phe-Ile, His-Pro-Phe-Leu, His-Pro-Phe-tert.-Leu, His-Pro-Phe-Lys, His-Pro-Phe-Met, His-Pro-Phe-Nbg, His-Pro-Phe-Nle, His-Pro-Phe-(N-Me-His), His-Pro-Phe-(N-Me-Phe), His-Pro-Phe-Orn, His-Pro-Phe-Pro, His-Pro-Phe-Ser, His-Pro-Phe-Thr, His-Pro-Phe-Tic, His-Pro-Phe-Trp, His-Pro-Phe-Tyr, His-Pro-Phe-Val, His-Pro-Pro-His, His-Pro-Ser-His, His-Pro-Thr-His, His-Pro-Tic-His, His-Pro-Trp-His, His-Pro-Tyr-His or His-Pro-Val-His.

E is preferably -CONH-, furthermore preferably -COO-, and in addition preferably -CSNH- or $-SO_2-$.

Y is preferably R^5, -CHA-COOA or $-CHA-CONR^7R^8$, and E-Y is also preferably morpholinocarbonyl.

The $-NR^2-CHR^3-CHOH-(CH_2)_n-NR^4-$ group is preferably $-NH-CHR^3-CHOH-CH_2-NH-$, in particular -NH-CH(cyclohexylmethyl)-$CHOH-CH_2-NH-$, furthermore $-NH-CH(CH_2CH_2$-cyclohexyl)-CHOH-CH_2-NH-, -NH-CH(isobutyl)-$CHOH-CH_2-NH-$ or -NH-CH(benzyl)-$CHOH-CH_2-NH-$. This group has at least one chiral centre. The compounds of the formula I can thus arise in various - optically inactive or optically active - forms. The formula I covers all these forms. For n = 1, the 2S-hydroxy-4S-amino enantiomers are preferred, and for n = 2,

correspondingly the 3S-hydroxy-4S-amino enantiomers.

Accordingly, the invention relates, in particular, to those compounds of the formula I in which at least one of the radicals mentioned has one of the preferred meanings specified above. Some preferred groups of compounds may be expressed through the following part formulae Ia to Id, which correspond to the formula I, but in which

in Ia X is H, ETOC, IPOC, BOC, POA, CBZ, ETNC, IPNC, MC, N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, acetyl, propionyl, isovaleryl, 2-phenylbutyryl, 2-benzyl-3-phenylpropionyl, PBB, 2-(2-phenylethyl)-4-phenylbutyryl, 2-(1-naphthylmethyl)-4-phenylbutyryl, benzoyl, ethylsulfonyl, isopropylsulfonyl or morpholinosulfonyl,
Z is His, Cal-His, Hph-His, αNal-His, βNal-His, Phe-Abu, Phe-Gly, Phe-His, Phe-N(im)-methyl-His, Phe-Leu, Phe-Met, Phe-Nle, Phe-Phe, Phe-Pyr or Phe-Trp,
R^2 and R^4 are H,
R^3 is butyl, isobutyl, cyclohexylmethyl, 2-cyclohexylethyl or benzyl, and
n is 1;

in Ib X is H, ETOC, IPOC, BOC, ETNC, IPNC, MC or PBB,
Z is His, Cal-His, Hph-His, αNal-His, βNal-His, Trp-His, Tyr-His, Phe-Abu, Phe-Gly, Phe-His, Phe-N(im)-methyl-His, Phe-Leu, Phe-Met, Phe-Nle, Phe-Phe, Phe-Pyr or Phe-Trp,
R^2 and R^4 are H,
R^3 is cyclohexylmethyl, and
n is 1;

in Ic X is H, IPOC, BOC or MC,
Z is Phe-Gly or Phe-His,
R^2 and R^4 are H,

R^3 is cyclohexylmethyl or benzyl, and
n is 1;

in Id X is BOC,
Z is Phe-His,
R^2 and R^4 are H,
R^3 is cyclohexylmethyl, and
n is 1.

Further preferred compounds of the formulae I' and Ia' to Id' are those which correspond to the formulae I and Ia to Id, but in which

E is -CONH-,
Y is A, phenyl, benzyl, cyclohexyl, CHA-$COOR^6$ or CHA-$CONR^7R^8$,
R^6 is alkyl having 1-4 carbon atoms,
R^7 is H,
R^8 is H or CH_2Het,
Het is 3-amino-5,6-dimethylpyrazin-2-yl, 5-tetrazolyl, pyridyl, pyridylmethyl, 2-hydroxy-4,6-dimethyl-3-pyridyl or 2-methyl-4-amino-5-pyrimidyl, and
A is alkyl having 1-5 carbon atoms, preferably isopropyl, isobutyl, sec.-butyl or isopentyl.

Further preferred compounds of the formulae I" and Ia" to Id" are those which correspond to the formulae I and Ia to Id, but in which

E is -COO-, and
Y is alkyl having 1-5 carbon atoms, benzyl or cyclohexyl.

Further preferred compounds of the formulae I"' and Ia"' to Id"' are those which correspond to the formulae I and Ia to Id, but in which

E-Y is alkylsulfonyl having 1-5 carbon atoms, phenylsulfonyl, benzylsulfonyl, cyclohexylsulfonyl, aminosulfonyl or morpholinosulfonyl.

In addition, preferred compounds are of the formulae I, Ia to Id, I', Ia' to Id', I", Ia" to Id", I"' and Ia"' to Id"', but in which one or more of the prerequisites below apply, namely in which

(a) X is other than BOC;
(b) X is ETOC, IPOC, POA, CBZ, ETNC, IPNC, MC, N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, acetyl, propionyl, isovaleryl, 2-phenylbutyryl, 2-benzyl-3-phenylpropionyl, PBB, 2-(2-phenylethyl)-4-phenylbutyryl, 2-(1-naphthylmethyl)-4-phenylbutyryl, benzoyl, ethylsulfonyl, isopropylsulfonyl or morpholinosulfonyl;
(c) X is IPOC;
(d) X is MC;
(e) Z is other than Phe-His;
(f) Z is Phe-Gly;
(g) R^3 is other than cyclohexylmethyl;
(h) R^3 is benzyl;
(i) E is -COO-;
(j) E is -CSNH-;
(k) E is $-SO_2-$;
(l) E is $-SO_2NH-$;
(m) E is -PO(OA)-O-;
(n) E-Y is -CO-NH-cyclohexyl;
(o) E-Y is $-CO-NH-(CHR^5)_s-COOR^6$;
(p) E-Y is $-CO-NH-(CHR^5)_s-CONR^7R^8$;
(q) E-Y is pyrrolidinocarbonyl, piperidinocarbonyl, morpholinocarbonyl, pyrrolidinosulfonyl, piperidinosulfonyl or morpholinosulfonyl.

The invention furthermore relates to a process for the preparation of an amino acid derivative of the formula I and its salts, characterized in that it is liberated from

one of its functional derivatives through treatment with a solvolysing or hydrogenolysing agent,

or in that a compound corresponding to the formula I, but containing one or more additional C-C and/or C-N and/or C-O bonds and/or O atoms in place of H atoms, is reduced,

or in that a carboxylic acid of the formula II

$$X\text{-}G^1\text{-}OH \qquad II$$

in which G^1 (a) is Z^1,
(b) is Z,

is reacted with an amino compound of the formula III

$$H\text{-}G^2 \qquad III$$

in which G^2 (a) is $-Z^2\text{-}NR^2\text{-}CHR^3\text{-}CHOH\text{-}(CH_2)_n\text{-}NR^4\text{-}E\text{-}Y$,
(b) is $-NR^2\text{-}CHR^3\text{-}CHOH\text{-}(CH_2)_n\text{-}NR^4\text{-}E\text{-}Y$, and

$Z^1 + Z^2$ together are Z,

and in that, if appropriate, in a compound of the formula I, a functionally derived amino and/or hydroxyl group is liberated by treatment with solvolysing or hydrogenolysing agents and/or a radical Y is converted into another radical Y through treatment with esterifying, solvolysing, acylating or amidating agents and/or a compound of the formula I is converted into one of its salts through treatment with an acid.

The compounds of the formula I and also the starting materials for their preparation are, in addition, prepared by methods which are known per se, as described in the literature (for example, in the standard works such as Houben-Weyl, Methoden der organischen Chemie [Methods of Organic Chemistry], Georg-Thieme-Verlag, Stuttgart; compare,

furthermore, EP-A-45,665, EP-A-77,028, EP-A-77,029, EP-A-81,783 and the other abovementioned publications), to be precise under reaction conditions which are known and suitable for the reactions mentioned. Use can also be made here of variants which are known per se, but not described here in greater detail.

If desired, the starting materials can also be formed in situ, so that they are not isolated from the reaction mixture, but instead further reacted immediately to form the compounds of the formula I.

The compounds of the formula I are preferably obtained by liberating them from their functional derivatives through solvolysis, in particular hydrolysis, or through hydrogenolysis.

Preferred starting materials for the solvolysis or hydrogenolysis are those which contain appropriately protected amino and/or hydroxyl groups in place of one or more free amino and/or hydroxyl groups, preferably those which carry an amino-protecting group in place of an H atom which is bonded to an N atom, for example those which correspond to the formula I, but contain an N(im)-R^9-His group (in which R^9 is an amino-protecting group, for example BOM or DNP) in place of a His group.

Furthermore, preferred starting materials are those which carry a hydroxyl-protecting group in place of the H atom of a hydroxyl group, for example those of the formula $X\text{-}Z\text{-}NR^2\text{-}CHR^3\text{-}CHOR^{10}\text{-}(CH_2)_n\text{-}NR^4\text{-}E\text{-}Y$ in which R^{10} is a hydroxyl-protecting group.

It is also possible for several - identical or different - protected amino and/or hydroxyl groups to be present in the molecule of the starting material. If the protecting groups present are different from one another, they may in many cases be removed selectively.

The term "amino-protecting group" is generally known and relates to groups which are suitable for protecting (blocking) an amino group against chemical reactions, but which can easily be removed after the chemical reaction desired has been carried out elsewhere in the molecule. Typical such groups are, in particular, unsubstituted or substituted acyl, aryl (for example DNP), aralkoxymethyl (for example BOM) or aralkyl (for example benzyl, 4-nitrobenzyl and triphenylmethyl) groups. Since the amino-protecting groups are removed after the reaction (or reaction sequence) desired, their type and size are, in addition, not critical; however, preferred such groups are those having 1-20, in particular 1-8, carbon atoms. In connection with the present process, the term "acyl group" should be taken in the broadest sense. It includes acyl groups which are derived from aliphatic, araliphatic, aromatic or heterocyclic carboxylic acids or sulfonic acids and, in particular, alkoxycarbonyl, aryloxycarbonyl and, above all, aralkoxycarbonyl groups. Examples of such acyl groups are alkanoyl, such as acetyl, propionyl or butyryl; aralkanoyl, such as phenylacetyl; aroyl, such as benzoyl or toluyl; aryloxyalkanoyl, such as POA; alkoxycarbonyl, such as methoxycarbonyl, ethoxycarbonyl, 2,2,2-trichloroethoxycarbonyl, BOC or 2-iodoethoxycarbonyl; and aralkyloxycarbonyl, such as CBZ ("carbobenzoxy"), 4-methoxybenzyloxycarbonyl or FMOC. Preferred amino-protecting groups are DNP and BOM, furthermore CBZ, FMOC, benzyl and acetyl.

The term "hydroxyl-protecting group" is likewise generally known and relates to groups which are suitable for protecting a hydroxyl group against chemical reactions, but which can easily be removed after the chemical reaction desired has been carried out elsewhere in the molecule. Typical such groups are the abovementioned unsubstituted or substituted aryl, aralkyl or acyl groups, furthermore also alkyl groups. The nature and size of the hydroxyl-protecting groups is not critical since they are removed

again after the chemical reaction or reaction sequence desired; preferred groups are those having 1-20, in particular 1-10, carbon atoms. Examples of hydroxyl-protecting groups are, inter alia, benzyl, p-nitrobenzoyl, p-toluenesulfonyl and acetyl, benzyl and acetyl being particularly preferred.

The functional derivatives, to be used as starting materials, of compounds of the formula I can be prepared by conventional methods of amino acid and peptide synthesis, as described, for example, in the standard works and patent applications mentioned.

The compounds of the formula I are liberated from their functional derivatives - depending on the protecting group used - for example, using strong acids, preferably using trifluoroacetic acid or perchloric acid, but alternatively other strong inorganic acids, such as hydrochloric acid or sulfuric acid, strong organic carboxylic acids, such as trichloroacetic acid, or sulfonic acids, such as benzene- or p-toluenesulfonic acid. The presence of an additional inert solvent is possible, but not always necessary. Suitable inert solvents are preferably organic, for example carboxylic acids, such as acetic acid, ethers, such as tetrahydrofuran or dioxane, amides, such as dimethylformamide (DMF), halogenated hydrocarbons, such as dichloromethane, furthermore also alcohols, such as methanol, ethanol or isopropanol, and also water. Mixtures of the abovementioned solvents are furthermore suitable. Trifluoroacetic acid is preferably used in excess without addition of a further solvent, and perchloric acid is preferably used in the form of a mixture of acetic acid and 70% perchloric acid in the ratio 9:1. The reaction temperatures for the cleavage are preferably between about 0 and about 50°, preferably between 15 and 30° (room temperature).

The BOC group can preferably be removed, for example,

using 40% trifluoroacetic acid in methylene chloride or using about 3 to 5 N HCl in dioxane at 15-30°, and the FMOC group using an approximately 5 to 20% solution of dimethylamine, diethylamine or piperidine in DMF at 15-30°. The DNP group is also removed, for example, using an approximately 3 to 10% solution of 2-mercaptoethanol in DMF/water at 15-30°.

Protecting groups which can be removed hydrogenolytically (for example BOM, CBZ or benzyl) can be removed, for example, through treatment with hydrogen in the presence of a catalyst (for example a noble-metal catalyst such as palladium, preferably on a support such as charcoal). Suitable solvents here are the abovementioned, in particular, for example, alcohols, such as methanol or ethanol, or amides, such as DMF. The hydrogenolysis is generally carried out at temperatures between about 0 and 100° and pressures between about 1 and 200 bar, preferably at 20-30° and 1-10 bar. Hydrogenolysis of the CBZ group is readily achieved, for example, on 5 to 10% Pd/C in methanol at 20-30°.

The compounds of the formula I can also be obtained by reducing corresponding compounds which contain one or more additional C-C and/or C-N and/or C-O bonds and/or O atoms in place of H atoms.

Thus, for example, amino compounds of the formula I which contain a substituent Ar = aminophenyl can be obtained by reducing the corresponding nitro compounds, for example by catalytic hydrogenation under the conditions mentioned above for hydrogenolysis.

Compounds of the formula I can also be obtained through direct peptide synthesis from a carboxylic acid (formula II) and an amine component (formula III). Suitable carboxylic acid components are, for example, those of the part formula X-Z-OH, and suitable amine components are

those of the part formula $H\text{-}NR^2\text{-}CHR^3\text{-}CHOH\text{-}(CH_2)_n\text{-}NR^4\text{-}E\text{-}Y$. However, the peptide bond can also be linked within the group Z; in this case, a carboxylic acid of the formula $X\text{-}Z^1\text{-}OH$ is reacted with an amino compound of the formula $H\text{-}Z^2\text{-}NR^2\text{-}CHR^3\text{-}CHOH\text{-}(CH_2)_n\text{-}NR^4\text{-}E\text{-}Y$ where $Z^1 + Z^2 = Z$. This reaction is preferably carried out by conventional methods of peptide synthesis, as described, for example, in Houben-Weyl, loc. cit., volume 15/II, pages 1 to 806 (1974).

The reaction is preferably carried out in the presence of a dehydrating agent, for example a carbodiimide such as DCCI or dimethylaminopropylethylcarbodiimide, furthermore propanephosphonic anhydride (compare Angew. Chem. 92, 129 (1980)), diphenylphosphoryl azide or 2-ethoxy-N-ethoxycarbonyl-1,2-dihydroquinoline, in an inert solvent, for example a halogenated hydrocarbon such as dichloromethane, an ether such as tetrahydrofuran or dioxane, an amide such as DMF or dimethylacetamide, or a nitrile such as acetonitrile, at temperatures between about -10 and 40, preferably between 0 and 30°.

In place of II or III, suitable reactive derivatives of these substances may alternatively be employed in the reaction, for example those in which reactive groups are temporarily blocked by protecting groups. The amino acid derivatives III can be used, for example, in the form of their activated esters, which are preferably formed in situ, for example by adding HOBt or N-hydroxysuccinimide.

The majority of the starting materials of the formulae II and III are known. If they are unknown, they can be prepared by known methods, for example the abovementioned methods of peptide synthesis and removal of protecting groups.

If desired, a functionally derived amino and/or hydroxyl group in a compound of the formula I can be liberated

through solvolysis or hydrogenolysis by one of the methods described above.

Thus, in particular, a compound of the formula I in which X is other than H can be converted into a compound of the formula I (X = H), preferably through hydrogenolysis if X is CBZ, otherwise through selective solvolysis. If X is BOC, the BOC group can be removed, for example, using HCl in dioxane at room temperature.

It is furthermore possible to convert a radical Y into another radical Y through treatment with esterifying, solvolysing, acylating or amidating agents. Thus, an acid can be esterified, for example, with the aid of an alcohol of the formula A-OH or a diazoalkane, for example diazomethane, or an ester can be saponified into the corresponding acid, for example using aqueous-dioxanic sodium hydroxide solution at room temperature. Furthermore, for example, an ester can be converted into the corresponding amide through treatment with ammonia or with an amine of the formula $A\text{-}NH_2$ or A_2NH.

A base of the formula I can be converted into the pertinent acid-addition salt using an acid. Suitable acids for this reaction are, in particular, those which give physiologically acceptable salts. Thus, inorganic acids, for example sulfuric acid, nitric acid, hydrohalic acids, such as hydrochloric acid or hydrobromic acid, phosphoric acids, such as orthophosphoric acid, or sulfamic acid, furthermore organic acids, in particular aliphatic, alicyclic, araliphatic, aromatic or heterocyclic monobasic or polybasic carboxylic, sulfonic or sulfuric acids, for example formic acid, acetic acid, propionic acid, pivalic acid, diethylacetic acid, malonic acid, succinic acid, pimelic acid, fumaric acid, maleic acid, lactic acid, tartaric acid, malic acid, benzoic acid, salicylic acid, 2- or 3-phenylpropionic acid, citric acid, gluconic acid, ascorbic acid, nicotinic acid, isonicotinic acid, methane-

or ethanesulfonic acid, ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, naphthalene-mono- and disulfonic acids, and laurylsulfuric acid may be used. Salts with physiologically unacceptable acids, for example picrates, can be used for isolating and/or purifying the compounds of the formula I.

The novel compounds of the formula I and their physiologically acceptable salts can be used for the preparation of pharmaceutical preparations by converting them into a suitable dosage form together with at least one excipient or adjuvant and, if desired, together with one or more further active ingredients. The preparations thus obtained can be employed as medicaments in human or veterinary medicine. Suitable excipients are organic or inorganic substances which are suitable for enteral (for example oral or rectal) or parenteral administration or for administration in the form of an inhalation spray and which do not react with the novel compounds, for example water, vegetable oils, benzyl alcohols, polyethylene glycols, glycerol triacetate and other fatty acid glycerides, gelatin, soybean lecithin, carbohydrates, such as lactose or starch, magnesium stearate, talc or cellulose. For oral administration, tablets, coated tablets, capsules, syrups, juices or drops are particularly used; specific lacquered tablets and capsules having gastric juice-resistant coatings or capsule shells are of interest. Rectal administration is effected by suppositories, and parenteral administration by solutions, preferably oily or aqueous solutions, furthermore suspensions, emulsions or implants. For administration as inhalation spray, sprays which contain the active ingredient either dissolved or suspended in a propellant gas mixture (for example fluorochlorohydrocarbons) can be used. The active ingredient is preferably used here in micronized form, where one or more additional physiologically acceptable solvents may be present, for example ethanol. Inhalation solutions can

be administered with the aid of conventional inhalers. The novel compounds can also be lyophilized, and the lyophilisates obtained can be used, for example, for the preparation of injection preparations. The preparations specified can be sterilized and/or contain adjuvants, such as preservatives, stabilizers and/or wetting agents, emulsifiers, salts for influencing the osmotic pressure, buffers, colorants and/or fragrances. If desired, they can also contain one or more further active ingredients, for example one or more vitamins.

The substances according to the invention are generally administered analogously to other known, commercially available peptides, but, in particular, analogously to the compounds described in EP-A-77,028, preferably in dosages between about 100 mg and 30 g, in particular between 500 mg and 5 g, per dosage unit. The daily dosage is preferably between about 2 and 600 mg/kg of body weight. However, the specific dose for each particular patient depends on a very wide variety of factors, for example on the activity of the specific compound employed, on the age, body weight, general health, sex, on the diet, on the point in time and method of administration, on the rate of excretion, medicament combination and severity of the respective disorder to which the therapy applies. Parenteral administration is preferred.

All temperatures above and below are specified in °C. In the following examples, "conventional work-up" denotes: if necessary, water is added to the mixture, which is neutralized and extracted with ether or dichloromethane, the phases are separated, the organic phase is dried over sodium sulfate, filtered and evaporated, and the product is purified by chromatography on silica gel and/or crystallization.

Example 1

A mixture of 1 g of N-isopentyl-N'-[2S-hydroxy-3S-(N-tert.-butoxycarbonyl-L-phenylalanyl-N(im)-(2,4-dinitrophenyl)-L-histidylamino)-4-cyclohexylbutyl]-urea [N-isopentyl-N'-[2S-hydroxy-3S-(BOC-Phe-(imi-DNP-His)-amino)-4-cyclohexylbutyl]-urea; obtainable by reaction of 1-bromo-3S-BOC-amino-4-cyclohexylbutan-2-one with NaN_3 in DMF at 0° to form 1-azido-3S-BOC-amino-4-cyclohexylbutan-2-one (melting point 58-59°), reduction using $NaBH_4$ with methanol to form 1-azido-3S-BOC-amino-4-cyclohexylbutan-2S-ol (melting point 170-171°; 1-azido-3S-BOC-amino-4-cyclohexylbutan-2R-ol, melting point 69-71° is also produced and is separated from the 2S-epimer by chromatography), hydrogenation on Pd/C in methanol to form 1-amino-3S-BOC-amino-4-cyclohexylbutan-2S-ol (melting point 110-111°; analogously: 1-amino-3S-BOC-amino-4-cyclohexylbutan-2R-ol, melting point 116-117°), reaction with isopentyl isocyanate in THF (2 hours at 20°) to form N-isopentyl-N'-(2S-hydroxy-3S-BOC-amino-4-cyclohexylbutyl)-urea (melting point 160-162°), removal of the BOC group using 4 N HCl in dioxane, reaction with BOC-(imi-DNP-His)-OH to form N-isopentyl-N'-[2S-hydroxy-3S-(BOC-(imi-DNP-His)-amino)-4-cyclohexylbutyl]-urea, re-removal of the BOC group and reaction with BOC-Phe-OH], 2 g of 2-mercaptoethanol, 20 ml of DMF and 20 ml of water is adjusted to pH 8 with stirring at 20° using aqueous Na_2CO_3 solution, and is stirred for 2 hours at 20°. After conventional work-up, N-isopentyl-N'-[2S-hydroxy-3S-(BOC-Phe-His-amino)-4-cyclohexylbutyl]-urea, melting point 132-134°, is obtained.

The following are obtained analogously through cleavage of the appropriate (imi-DNP-His) derivatives:

N-(2S-hydroxy-3S-BOC-αNal-His-amino-4-cyclohexylbutyl)-urea [melting point 134°; via N-[2S-hydroxy-3S-BOC-(imi-DNP-His)-amino-4-cyclohexylbutyl]-urea [melting point 82°

(decomposition)] and N-[2S-hydroxy-3S-BOC-αNal-(imi-DNP-His)-amino-4-cyclohexylbutyl]-urea (melting point 107-108°)].

N-[2S-Hydroxy-3S-(BOC-Phe-His-amino)-4-cyclohexylbutyl]-urea [melting point 156°; through reaction of 2S-tert.-butyl-dimethylsilyloxy-3S-BOC-amino-4-cyclohexylbutylamine with trimethylsilyl isocyanate in THF to give N-(2S-tert.-butyldimethylsilyloxy-3S-BOC-amino-4-cyclohexylbutyl)-urea (melting point 61°) and further via N-[2S-hydroxy-3S-BOC-(imi-DNP-His)-amino-4-cyclohexylbutyl]-urea and N-[2S-hydroxy-3S-BOC-Phe-(imi-DNP-His)-amino-4-cyclohexylbutyl]-urea]

N-methyl-N'-[2S-hydroxy-3S-(BOC-Phe-His-amino)-4-cyclo-hexylbutyl]-urea

N-methyl-N'-[2S-hydroxy-3S-(BOC-Phe-His-amino)-4-cyclo-hexylbutyl]-urea

N-ethyl-N'-[2S-hydroxy-3S-(BOC-Phe-His-amino)-4-cyclo-hexylbutyl]-urea

N-propyl-N'-[2S-hydroxy-3S-(BOC-Phe-His-amino)-4-cyclo-hexylbutyl]-urea

N-isopropyl-N'-[2S-hydroxy-3S-(PBB-His-amino)-4-cyclo-hexylbutyl]-urea

N-isopropyl-N'-[2S-hydroxy-3S-(POA-His-amino)-4-cyclo-hexylbutyl]-urea

N-isopropyl-N'-[2S-hydroxy-3S-(PBB-Phe-His-amino)-4-cyclohexylbutyl]-urea

N-isopropyl-N'-[2S-hydroxy-3S-(ETOC-Phe-His-amino)-4-cyclohexylbutyl]-urea

N-isopropyl-N'-[2S-hydroxy-3S-(IPOC-Phe-His-amino)-4-cyclohexylbutyl]-urea, melting point 206-208°

N-isopropyl-N'-[2S-hydroxy-3S-(BOC-Phe-His-amino)-4-cyclohexylbutyl]-urea

N-isopropyl-N'-[2S-hydroxy-3S-(CBZ-Phe-His-amino)-4-cyclohexylbutyl]-urea

N-isopropyl-N'-[2S-hydroxy-3S-(ETNC-Phe-His-amino)-4-cyclohexylbutyl]-urea

N-isopropyl-N'-[2S-hydroxy-3S-(IPNC-Phe-His-amino)-4-cyclohexylbutyl]-urea

N-isopropyl-N'-[2S-hydroxy-3S-(N,N-dimethylcarbamoyl-Phe-His-amino)-4-cyclohexylbutyl]-urea

N-isopropyl-N'-[2S-hydroxy-3S-(N,N-diethylcarbamoyl-Phe-His-amino)-4-cyclohexylbutyl]-urea

N-isopropyl-N'-[2S-hydroxy-3S-(MC-Phe-His-amino)-4-cyclohexylbutyl]-urea

N-isopropyl-N'-[2S-hydroxy-3S-(acetyl-Phe-His-amino)-4-cyclohexylbutyl]-urea

N-isopropyl-N'-[2S-hydroxy-3S-(propionyl-Phe-His-amino)-4-cyclohexylbutyl]-urea

N-isopropyl-N'-[2S-hydroxy-3S-(isovaleryl-Phe-His-amino)-4-cyclohexylbutyl]-urea

N-isopropyl-N'-[2S-hydroxy-3S-(benzoyl-Phe-His-amino)-4-cyclohexylbutyl]-urea

N-isopropyl-N'-[2S-hydroxy-3S-(POA-Phe-His-amino)-4-cyclohexylbutyl]-urea

N-isopropyl-N'-[2S-hydroxy-3S-(ethylsulfonyl-Phe-His-amino)-4-cyclohexylbutyl]-urea

N-isopropyl-N'-[2S-hydroxy-3S-(isopropylsulfonyl-Phe-His-amino)-4-cyclohexylbutyl]-urea

N-isopropyl-N'-[2S-hydroxy-3S-(morpholinosulfonyl-Phe-His-amino)-4-cyclohexylbutyl]-urea

N-isobutyl-N'-[2S-hydroxy-3S-(BOC-Phe-His-amino)-4-cyclohexylbutyl]-urea

N-sec.-butyl-N'-[2S-hydroxy-3S-(BOC-Phe-His-amino)-4-cyclohexylbutyl]-urea, melting point 199°, (decomposition)

N-(2-methylbutyl)-N'-[2S-hydroxy-3S-(BOC-Phe-His-amino)-4-cyclohexylbutyl]-urea

N-isopentyl-N'-[2S-hydroxy-3S-(PBB-His-amino)-4-cyclohexylbutyl]-urea

N-isopentyl-N'-[2S-hydroxy-3S-(POA-His-amino)-4-cyclohexylbutyl]-urea

N-isopentyl-N'-[2S-hydroxy-3S-(PBB-Phe-His-amino)-4-cyclohexylbutyl]-urea

N-isopentyl-N'-[2S-hydroxy-3S-(ETOC-Phe-His-amino)-4-cyclohexylbutyl]-urea

N-isopentyl-N'-[2S-hydroxy-3S-(IPOC-Phe-His-amino)-4-cyclohexylbutyl]-urea

N-isopentyl-N'-[2S-hydroxy-3S-(CBZ-Phe-His-amino)-4-cyclohexylbutyl]-urea

N-isopentyl-N'-[2S-hydroxy-3S-(ETNC-Phe-His-amino)-4-cyclohexylbutyl]-urea

N-isopentyl-N'-[2S-hydroxy-3S-(IPNC-Phe-His-amino)-4-cyclohexylbutyl]-urea

N-isopentyl-N'-[2S-hydroxy-3S-(N,N-dimethylcarbamoyl-Phe-His-amino)-4-cyclohexylbutyl]-urea

N-isopentyl-N'-[2S-hydroxy-3S-(N,N-diethylcarbamoyl-Phe-His-amino)-4-cyclohexylbutyl]-urea

N-isopentyl-N'-[2S-hydroxy-3S-(MC-Phe-His-amino)-4-cyclohexylbutyl]-urea

N-isopentyl-N'-[2S-hydroxy-3S-(acetyl-Phe-His-amino)-4-cyclohexylbutyl]-urea

N-isopentyl-N'-[2S-hydroxy-3S-(propionyl-Phe-His-amino)-4-cyclohexylbutyl]-urea

N-isopentyl-N'-[2S-hydroxy-3S-(isovaleryl-Phe-His-amino)-4-cyclohexylbutyl]-urea

N-isopentyl-N'-[2S-hydroxy-3S-(benzoyl-Phe-His-amino)-4-cyclohexylbutyl]-urea

N-isopentyl-N'-[2S-hydroxy-3S-(POA-Phe-His-amino)-4-cyclohexylbutyl]-urea

N-isopentyl-N'-[2S-hydroxy-3S-(ethylsulfonyl-Phe-His-amino)-4-cyclohexylbutyl]-urea

N-isopentyl-N'-[2S-hydroxy-3S-(isopropylsulfonyl-Phe-His-amino)-4-cyclohexylbutyl]-urea

N-isopentyl-N'-[2S-hydroxy-3S-(morpholinosulfonyl-Phe-His-amino)-4-cyclohexylbutyl]-urea

N-cyclohexyl-N'-[2S-hydroxy-3S-(IPOC-Phe-His-amino)-4-cyclohexylbutyl]-urea, melting point 189° [decomposition; via N-cyclohexyl-N'-[2S-hydroxy-3S-BOC-(imi-DNP-His)-amino)-4-cyclohexylbutyl]-urea [melting point 80° (decomposition)] and N-cyclohexyl-N'-[2S-hydroxy-3S-IPOC-Phe-(imi-DNP-His)-amino-4-cyclohexylbutyl]-urea [melting point 182° (decom-position)]]

N-cyclohexyl-N'-[2S-hydroxy-3S-(BOC-Phe-His-amino)-4-cyclohexylbutyl]-urea, melting point 146° [decomposition; via 2S-tert.-butyldimethylsilyloxy-3S-BOC-amino-4-cyclo-

hexylbutylamine (oil), N-cyclohexyl-N'-(2S-tert.-butyldimethylsilyloxy-3S-BOC-amino-4-cyclohexylbutyl)-urea (melting point 75-76°), N-cyclohexyl-N'-[2S-hydroxy-3S-BOC-(imi-DNP-His)-amino-4-cyclohexylbutyl]-urea [melting point 80° (decomposition)] and N-cyclohexyl-N'-[2S-hydroxy-3S-BOC-Phe-(imi-DNP-His)-amino-4-cyclohexylbutyl]-urea [melting point 154° (decomposition)]]

N-phenyl-N'-[2S-hydroxy-3S-(BOC-Phe-His-amino)-4-cyclohexylbutyl]-urea

N,N-(3-oxapentamethylene)-N'-[2S-hydroxy-3S-(BOC-Phe-His-amino)-4-cyclohexylbutyl]-urea

N-[2R-hydroxy-3S-(BOC-Phe-His-amino)-4-cyclohexylbutyl]-urea

N-methyl-N'-[2R-hydroxy-3S-(BOC-Phe-His-amino)-4-cyclohexylbutyl]-urea

N-ethyl-N'-[2R-hydroxy-3S-(BOC-Phe-His-amino)-4-cyclohexylbutyl]-urea

N-propyl-N'-[2R-hydroxy-3S-(BOC-Phe-His-amino)-4-cyclohexylbutyl]-urea

N-isopropyl-N'-[2R-hydroxy-3S-(PBB-His-amino)-4-cyclohexylbutyl]-urea

N-isopropyl-N'-[2R-hydroxy-3S-(POA-His-amino)-4-cyclohexylbutyl]-urea

N-isopropyl-N'-[2R-hydroxy-3S-(PBB-Phe-His-amino)-4-cyclohexylbutyl]-urea

N-isopropyl-N'-[2R-hydroxy-3S-(ETOC-Phe-His-amino)-4-cyclohexylbutyl]-urea

N-isopropyl-N'-[2R-hydroxy-3S-(IPOC-Phe-His-amino)-4-cyclohexylbutyl]-urea

N-isopropyl-N'-[2R-hydroxy-3S-(BOC-Phe-His-amino)-4-cyclohexylbutyl]-urea, melting point 139°

N-isopropyl-N'-[2R-hydroxy-3S-(CBZ-Phe-His-amino)-4-cyclohexylbutyl]-urea

N-isopropyl-N'-[2R-hydroxy-3S-(ETNC-Phe-His-amino)-4-cyclohexylbutyl]-urea

N-isopropyl-N'-[2R-hydroxy-3S-(IPNC-Phe-His-amino)-4-cyclohexylbutyl]-urea

N-isopropyl-N'-[2R-hydroxy-3S-(N,N-dimethylcarbamoyl-Phe-

His-amino)-4-cyclohexylbutyl]-urea
N-isopropyl-N'-[2R-hydroxy-3S-(N,N-diethylcarbamoyl-Phe-His-amino)-4-cyclohexylbutyl]-urea
N-isopropyl-N'-[2R-hydroxy-3S-(MC-Phe-His-amino)-4-cyclohexylbutyl]-urea
N-isopropyl-N'-[2R-hydroxy-3S-(acetyl-Phe-His-amino)-4-cyclohexylbutyl]-urea
N-isopropyl-N'-[2R-hydroxy-3S-(propionyl-Phe-His-amino)-4-cyclohexylbutyl]-urea
N-isopropyl-N'-[2R-hydroxy-3S-(isovaleryl-Phe-His-amino)-4-cyclohexylbutyl]-urea
N-isopropyl-N'-[2R-hydroxy-3S-(benzoyl-Phe-His-amino)-4-cyclohexylbutyl]-urea
N-isopropyl-N'-[2R-hydroxy-3S-(POA-Phe-His-amino)-4-cyclohexylbutyl]-urea
N-isopropyl-N'-[2R-hydroxy-3S-(ethylsulfonyl-Phe-His-amino)-4-cyclohexylbutyl]-urea
N-isopropyl-N'-[2R-hydroxy-3S-(isopropylsulfonyl-Phe-His-amino)-4-cyclohexylbutyl]-urea
N-isopropyl-N'-[2R-hydroxy-3S-(morpholinosulfonyl-Phe-His-amino)-4-cyclohexylbutyl]-urea
N-isobutyl-N'-[2R-hydroxy-3S-(BOC-Phe-His-amino)-4-cyclohexylbutyl]-urea
N-sec.-butyl-N'-[2R-hydroxy-3S-(BOC-Phe-His-amino)-4-cyclohexylbutyl]-urea
N-(2-methylbutyl)-N'-[2R-hydroxy-3S-(BOC-Phe-His-amino)-4-cyclohexylbutyl]-urea
N-isopentyl-N'-[2R-hydroxy-3S-(PBB-His-amino)-4-cyclohexylbutyl]-urea
N-isopentyl-N'-[2R-hydroxy-3S-(POA-His-amino)-4-cyclohexylbutyl]-urea
N-isopentyl-N'-[2R-hydroxy-3S-(PBB-Phe-His-amino)-4-cyclohexylbutyl]-urea
N-isopentyl-N'-[2R-hydroxy-3S-(ETOC-Phe-His-amino)-4-cyclohexylbutyl]-urea
N-isopentyl-N'-[2R-hydroxy-3S-(IPOC-Phe-His-amino)-4-cyclohexylbutyl]-urea
N-isopentyl-N'-[2R-hydroxy-3S-(BOC-Phe-His-amino)-4-

cyclohexylbutyl]-urea
N-isopentyl-N'-[2R-hydroxy-3S-(CBZ-Phe-His-amino)-4-cyclohexylbutyl]-urea
N-isopentyl-N'-[2R-hydroxy-3S-(ETNC-Phe-His-amino)-4-cyclohexylbutyl]-urea
N-isopentyl-N'-[2R-hydroxy-3S-(IPNC-Phe-His-amino)-4-cyclohexylbutyl]-urea
N-isopentyl-N'-[2R-hydroxy-3S-(N,N-dimethylcarbamoyl-Phe-His-amino)-4-cyclohexylbutyl]-urea
N-isopentyl-N'-[2R-hydroxy-3S-(N,N-diethylcarbamoyl-Phe-His-amino)-4-cyclohexylbutyl]-urea
N-isopentyl-N'-[2R-hydroxy-3S-(MC-Phe-His-amino)-4-cyclohexylbutyl]-urea
N-isopentyl-N'-[2R-hydroxy-3S-(acetyl-Phe-His-amino)-4-cyclohexylbutyl]-urea
N-isopentyl-N'-[2R-hydroxy-3S-(propionyl-Phe-His-amino)-4-cyclohexylbutyl]-urea
N-isopentyl-N'-[2R-hydroxy-3S-(isovaleryl-Phe-His-amino)-4-cyclohexylbutyl]-urea
N-isopentyl-N'-[2R-hydroxy-3S-(benzoyl-Phe-His-amino)-4-cyclohexylbutyl]-urea
N-isopentyl-N'-[2R-hydroxy-3S-(POA-Phe-His-amino)-4-cyclohexylbutyl]-urea
N-isopentyl-N'-[2R-hydroxy-3S-(ethylsulfonyl-Phe-His-amino)-4-cyclohexylbutyl]-urea
N-isopentyl-N'-[2R-hydroxy-3S-(isopropylsulfonyl-Phe-His-amino)-4-cyclohexylbutyl]-urea
N-isopentyl-N'-[2R-hydroxy-3S-(morpholinosulfonyl-Phe-His-amino)-4-cyclohexylbutyl]-urea
N-cyclohexyl-N'-[2R-hydroxy-3S-(IPOC-Phe-His-amino)-4-cyclohexylbutyl]-urea
N-cyclohexyl-N'-[2R-hydroxy-3S-(BOC-Phe-His-amino)-4-cyclohexylbutyl]-urea
N-phenyl-N'-(2R-hydroxy-3S-(BOC-Phe-His-amino)-4-cyclohexylbutyl]-urea
N,N-(3-oxapentamethylene)-N'-[2R-hydroxy-3S-(BOC-Phe-His-amino)-4-cyclohexylbutyl]-urea
N-[2S-hydroxy-3S-(BOC-Phe-His-amino)-4-cyclohexylbutyl]-

isopropylsulfonamide [melting point 117° (decomposition); via N-[2S-hydroxy-3S-BOC-(imi-DNP-His)-amino-4-cyclohexylbutyl]-isopropylsulfonamide] melting point 87° (decomposition)] and N-[2S-hydroxy-3S-BOC-Phe-(imi-DNP-His)-amino-4-cyclohexylbutyl]-isopropylsulfonamide (melting point 130°)].

Example 2

1 g of N-isopentyl-N'-[2S-hydroxy-3S-BOC-Phe-(imi-BOM-His)-amino-4-cyclohexylbutyl]-urea [obtainable through reaction of N-isopentyl-N'-(2S-hydroxy-3S-amino-4-cyclohexylbutyl)-urea with BOC-(imi-BOM-His)-OH to give N-isopentyl-N'-[2S-hydroxy-3S-BOC-(imi-BOM-His)-amino-4-cyclohexylbutyl]-urea, removal of the BOC group and reaction with BOC-Phe-OH] is dissolved in 10 ml of methanol, the solution is hydrogenated on 5% strength Pd/C at 20° and 1 bar to completion, the mixture is filtered, the filtrate is evaporated, and N-isopentyl-N'-[2S-hydroxy-3S-(BOC-Phe-His-amino)-4-cyclohexylbutyl]-urea, melting point 132-134°, is obtained.

The following are obtained analogously through hydrogenolysis of the appropriate imi-BOM-His compounds:

N-isopropyl-N'-[2R-hydroxy-3S-(BOC-Phe-His-amino)-4-cyclohexylbutyl]-urea, melting point 139° [via N-isopropyl-N'-[2R-hydroxy-3S-BOC-(imi-BOM-His)-amino-4-cyclohexylbutyl]-urea [melting point 214° (decomposition)] and N-isopropyl-N'-[2R-hydroxy-3S-BOC-Phe-(imi-BOM-His)-amino-4-cyclohexylbutyl]-urea (melting point 104°)];

N-isopropyl-N'-[2S-hydroxy-3S-(IPOC-Phe-His-amino)-4-cyclohexylbutyl]-urea, melting point 206-208° [via N-isopropyl-N'-[2S-tert.-butyldimethylsilyloxy-3S-BOC-amino-4-cyclohexylbutyl)-urea (melting point 131°) and N-isopropyl-N'-[2S-hydroxy-3S-BOC-(imi-BOM-His)-amino-4-cyclohexylbutyl]-urea [melting point 184° (decomposition)]];

N-isopropyl-N'-[2R-hydroxy-3S-(MC-Phe-His-amino)-4-cyclohexylbutyl]-urea, melting point 152° [decomposition; via N-isopropyl-N-(2R-hydroxy-3S-amino-4-cyclohexylbutyl)-urea (hydrochloride, melting point 84°), N-isopropyl-N'-[2R-hydroxy-3S-BOC-(imi-BOM-His)-amino-4-cyclohexylbutyl]-urea [melting point 214° (decomposition)] and N-isopropyl-N'-[2R-hydroxy-3S-Mc-Phe-(imi-BOM-His)-amino-4-cyclohexylbutyl]-urea [melting point 79° (decomposition)];

N-isopropyl-N'-[2S-hydroxy-3S-(ETOC-Phe-His-amino)-heptyl]-urea

N-isopropyl-N'-[2S-hydroxy-3S-(IPOC-Phe-His-amino)-heptyl]-urea

N-isopropyl-N'-[2S-hydroxy-3S-(BOC-Phe-His-amino)-heptyl]-urea

N-isopropyl-N'-[2S-hydroxy-3S-(ETNC-Phe-His-amino)-heptyl]-urea

N-isopropyl-N'-[2S-hydroxy-3S-(IPNC-Phe-His-amino)-heptyl]-urea

N-isopropyl-N'-[2S-hydroxy-3S-(MC-Phe-His-amino)-heptyl]-urea

N-isopropyl-N'-[2S-hydroxy-3S-(ETOC-Phe-His-amino)-5-methylhexyl]-urea

N-isopropyl-N'-[2S-hydroxy-3S-(IPOC-Phe-His-amino)-5-methylhexyl]-urea

N-isopropyl-N'-[2S-hydroxy-3S-(BOC-Phe-His-amino)-5-methylhexyl]-urea

N-isopropyl-N'-[2S-hydroxy-3S-(ETNC-Phe-His-amino)-5-methylhexyl]-urea

N-isopropyl-N'-[2S-hydroxy-3S-(IPNC-Phe-His-amino)-5-methylhexyl]-urea

N-isopropyl-N'-[2S-hydroxy-3S-(MC-Phe-His-amino)-5-methylhexyl]-urea

N-isopropyl-N'-[2S-hydroxy-3S-(ETOC-Phe-His-amino)-4-phenylbutyl]-urea

N-isopropyl-N'-[2S-hydroxy-3S-(IPOC-Phe-His-amino)-4-phenylbutyl]-urea

N-isopropyl-N'-[2S-hydroxy-3S-(BOC-Phe-His-amino)-4-

phenylbutyl]-urea, melting point 208° (decomposition)
N-isopropyl-N'-[2S-hydroxy-3S-(ETNC-Phe-His-amino)-4-phenylbutyl]-urea
N-isopropyl-N'-[2S-hydroxy-3S-(IPNC-Phe-His-amino)-4-phenylbutyl]-urea
N-isopropyl-N'-[2S-hydroxy-3S-(MC-Phe-His-amino)-4-phenylbutyl]-urea

N-isopentyl-N'-[2S-hydroxy-3S-(ETOC-Phe-His-amino)-heptyl]-urea
N-isopentyl-N'-[2S-hydroxy-3S-(IPOC-Phe-His-amino)-heptyl]-urea
N-isopentyl-N'-[2S-hydroxy-3S-(BOC-Phe-His-amino)-heptyl]-urea
N-isopentyl-N'-[2S-hydroxy-3S-(ETNC-Phe-His-amino)-heptyl]-urea
N-isopentyl-N'-[2S-hydroxy-3S-(IPNC-Phe-His-amino)-heptyl]-urea
N-isopentyl-N'-[2S-hydroxy-3S-(MC-Phe-His-amino)-heptyl]-urea
N-isopentyl-N'-[2S-hydroxy-3S-(ETOC-Phe-His-amino)-5-methylhexyl]-urea
N-isopentyl-N'-[2S-hydroxy-3S-(IPOC-Phe-His-amino)-5-methylhexyl]-urea
N-isopentyl-N'-[2S-hydroxy-3S-(BOC-Phe-His-amino)-5-methylhexyl]-urea
N-isopentyl-N'-[2S-hydroxy-3S-(ETNC-Phe-His-amino)-5-methylhexyl]-urea
N-isopentyl-N'-[2S-hydroxy-3S-(IPNC-Phe-His-amino)-5-methylhexyl]-urea
N-isopentyl-N'-[2S-hydroxy-3S-(MC-Phe-His-amino)-5-methylhexyl]-urea
N-isopentyl-N'-[2S-hydroxy-3S-(ETOC-Phe-His-amino)-4-phenylbutyl]-urea
N-isopentyl-N'-[2S-hydroxy-3S-(IPOC-Phe-His-amino)-4-phenylbutyl]-urea
N-isopentyl-N'-[2S-hydroxy-3S-(BOC-Phe-His-amino)-4-phenylbutyl]-urea

N-isopentyl-N'-[2S-hydroxy-3S-(ETNC-Phe-His-amino)-4-phenylbutyl]-urea

N-isopentyl-N'-[2S-hydroxy-3S-(IPNC-Phe-His-amino)-4-phenylbutyl]-urea

N-isopentyl-N'-[2S-hydroxy-3S-(MC-Phe-His-amino)-4-phenylbutyl]-urea

N-isopropyl-N'-[2S-hydroxy-3S-(BOC-Cal-His-amino)-4-cyclohexylbutyl]-urea

N-isopropyl-N'-[2S-hydroxy-3S-(MC-Cal-His-amino)-4-cyclohexylbutyl]-urea

N-isopropyl-N'-[2S-hydroxy-3S-(BOC-Hph-His-amino)-4-cyclohexylbutyl]-urea

N-isopropyl-N'-[2S-hydroxy-3S-(MC-Hph-His-amino)-4-cyclohexylbutyl]-urea

N-isopropyl-N'-[2S-hydroxy-3S-(BOC-αNal-His-amino)-4-cyclohexylbutyl]-urea

N-isopropyl-N'-[2S-hydroxy-3S-(MC-αNal-His-amino)-4-cyclohexylbutyl]-urea

N-isopropyl-N'-[2S-hydroxy-3S-(BOC-βNal-His-amino)-4-cyclohexylbutyl]-urea

N-isopropyl-N'-[2S-hydroxy-3S-(MC-βNal-His-amino)-4-cyclohexylbuty]-urea

N-isopropyl-N' [2S-hydroxy-3S-(BOC-Trp-His-amino)-4-cyclohexylbutyl]-urea

N-isopropyl-N'-[2S-hydroxy-3S-(MC-Trp-His-amino)-4-cyclohexylbutyl]-urea

N-isopropyl-N'-[2S-hydroxy-3S-(BOC-Tyr-His-amino)-4-cyclohexylbutyl]-urea

N-isopropyl-N'-[2S-hydroxy-3S-(MC-Tyr-His-amino)-4-cyclohexylbutyl]-urea

N-isopentyl-N'-[2S-hydroxy-3S-(BOC-Cal-His-amino)-4-cyclohexylbutyl]-urea

N-isopentyl-N'-[2S-hydroxy-3S-(MC-Cal-His-amino)-4-cyclohexylbutyl]-urea

N-isopentyl-N'-[2S-hydroxy-3S-(BOC-Hph-His-amino)-4-cyclohexylbutyl]-urea

N-isopentyl-N'-[2S-hydroxy-3S-(MC-Hph-His-amino)-4-cyclo-

hexylbutyl]-urea
N-isopentyl-N'-[2S-hydroxy-3S-(BOC-αNal-His-amino)-4-cyclohexylbutyl]-urea
N-isopentyl-N'-[2S-hydroxy-3S-(MC-αNal-His-amino)-4-cyclohexylbutyl]-urea
N-isopentyl-N'-[2S-hydroxy-3S-(BOC-βNal-His-amino)-4-cyclohexylbutyl]-urea
N-isopentyl-N'-[2S-hydroxy-3S-(MC-βNal-His-amino)-4-cyclohexylbutyl]-urea
N-isopentyl-N'-[2S-hydroxy-3S-(BOC-Trp-His-amino)-4-cyclohexylbutyl]-urea
N-isopentyl-N'-[2S-hydroxy-3S-(MC-Trp-His-amino)-4-cyclohexylbutyl]-urea
N-isopentyl-N'-[2S-hydroxy-3S-(BOC-Tyr-His-amino)-4-cyclohexylbutyl]-urea
N-isopentyl-N'-[2S-hydroxy-3S-(MC-Tyr-His-amino)-4-cyclohexylbutyl]-urea
diethyl N-(2S-hydroxy-3S-MC-Phe-His-amino-4-cyclohexylbutyl)-phosphate monoamide.

Example 3

Isopropyl N-[2S-hydroxy-3S-(MC-Phe-His-amino)-4-cyclohexylbutyl]-carbamate, melting point 90-92°, is obtained analogously to Example 2 from isopropyl N-[2S-hydroxy-3S-MC-Phe-(imi-BOM-His)-amino-4-cyclohexylbutyl]-carbamate [melting point 101-105°; obtainable through reaction of 1-amino-3S-BOC-amino-4-cyclohexylbutan-2S-ol with isopropyl chloroformate to give isopropyl N-[2S-hydroxy-3S-BOC-amino-4-cyclohexylbutyl]-carbamate, removal of the BOC group, reaction with BOC-(imi-BOM-His)-OH to give isopropyl N-[2S-hydroxy-3S-BOC-(imi-BOM-His)-amino-4-cyclohexylbutyl]-carbamate, re-removal of the BOC group and reaction with MC-Phe-OH].

Isopropyl N-[2S-hydroxy-3S-BOC-Phe-His-amino-4-cyclohexylbutyl]-carbamate, melting point 170°, is obtained analogously from isopropyl N-[2S-hydroxy-3S-BOC-Phe-(imi-

BOM-His)-amino-4-cyclohexylbutyl]-carbamate (melting point 119-122°).

The following are obtained analogously:

ethyl N-[2S-hydroxy-3S-(ETOC-Phe-His-amino)-4-cyclohexylbutyl]-carbamate

ethyl N-[2S-hydroxy-3S-(IPOC-Phe-His-amino)-4-cyclohexylbutyl]-carbamate

ethyl N-[2S-hydroxy-3S-(BOC-Phe-His-amino)-4-cyclohexylbutyl]-carbamate

ethyl N-[2S-hydroxy-3S-(ETNC-Phe-His-amino)-4-cyclohexylbutyl]-carbamate

ethyl N-[2S-hydroxy-3S-(IPNC-Phe-His-amino)-4-cyclohexylbutyl]-carbamate

ethyl N-[2S-hydroxy-3S-(MC-Phe-His-amino)-4-cyclohexylbutyl]-carbamate

isopropyl N-[2S-hydroxy-3S-(ETOC-Phe-His-amino)-4-cyclohexylbutyl]-carbamate

isopropyl N-[2S-hydroxy-3S-(IPOC-Phe-His-amino)-4-cyclohexylbutyl]-carbamate

isopropyl N-[2S-hydroxy-3S-(ETNC-Phe-His-amino)-4-cyclohexylbutyl]-carbamate

isopropyl N-[2S-hydroxy-3S-(IPNC-Phe-His-amino)-4-cyclohexylbutyl]-carbamate

isopropyl N-[2S-hydroxy-3S-(N,N-dimethylcarbamoyl-Phe-His-amino)-4-cyclohexylbutyl]-carbamate

isopropyl N-[2S-hydroxy-3S-(N,N-diethylcarbamoyl-Phe-His-amino)-4-cyclohexylbutyl]-carbamate

isopropyl N-[2S-hydroxy-3S-(isopropylsulfonyl-Phe-His-amino)-4-cyclohexylbutyl]-carbamate

isopropyl N-[2S-hydroxy-3S-(morpholinosulfonyl-Phe-His-amino)-4-cyclohexylbutyl]-carbamate

isobutyl N-[2S-hydroxy-3S-(ETOC-Phe-His-amino)-4-cyclohexylbutyl]-carbamate

isobutyl N-[2S-hydroxy-3S-(IPOC-Phe-His amino)-4-cyclohexylbutyl]-carbamate

isobutyl N-[2S-hydroxy-3S-(BOC-Phe-His amino)-4-cyclohexylbutyl]-carbamate, melting point 147-149°

isobutyl N-[2S-hydroxy-3S-(ETNC-Phe-His-amino)-4-cyclohexylbutyl]-carbamate

isobutyl N-[2S-hydroxy-3S-(IPNC-Phe-His-amino)-4-cyclohexylbutyl]-carbamate

isobutyl N-[2S-hydroxy-3S-(MC-Phe-His-amino)-4-cyclohexylbutyl]-carbamate

isopentyl N-[2S-hydroxy-3S-(ETOC-Phe-His-amino)-4-cyclohexylbutyl]-carbamate

isopentyl N-[2S-hydroxy-3S-(IPOC-Phe-His-amino)-4-cyclohexylbutyl]-carbamate

isopentyl N-[2S-hydroxy-3S-(BOC-Phe-His-amino)-4-cyclohexylbutyl]-carbamate

isopentyl N-[2S-hydroxy-3S-(ETNC-Phe-His-amino)-4-cyclohexylbutyl]-carbamate

isopentyl N-[2S-hydroxy-3S-(IPNC-Phe-His-amino)-4-cyclohexylbutyl]-carbamate

isopentyl N-[2S-hydroxy-3S-(MC-Phe-His-amino)-4-cyclohexylbutyl]-carbamate

cyclohexyl N-[2S-hydroxy-3S-(ETOC-Phe-His-amino)-4-cyclohexylbutyl]-carbamate

cyclohexyl N-[2S-hydroxy-3S-(IPOC-Phe-His-amino)-4-cyclohexylbutyl]-carbamate

cyclohexyl N-[2S-hydroxy-3S-(BOC-Phe-His-amino)-4-cyclohexylbutyl]-carbamate

cyclohexyl N-[2S-hydroxy-3S-(ETNC-Phe-His-amino)-4-cyclohexylbutyl]-carbamate

cyclohexyl N-[2S-hydroxy-3S-(IPNC-Phe-His-amino)-4-cyclohexylbutyl]-carbamate

cyclohexyl N-[2S-hydroxy-3S-(MC-Phe-His-amino)-4-cyclohexylbutyl]-carbamate

benzyl N-[2S-hydroxy-3S-(ETOC-Phe-His-amino)-4-cyclo-

hexylbutyl]-carbamate
benzyl N-[2S-hydroxy-3S-(IPOC-Phe-His-amino)-4-cyclo-hexylbutyl]-carbamate
benzyl N-[2S-hydroxy-3S-(BOC-Phe-His-amino)-4-cyclo-hexylbutyl]-carbamate
benzyl N-[2S-hydroxy-3S-(ETNC-Phe-His-amino)-4-cyclo-hexylbutyl]-carbamate
benzyl N-[2S-hydroxy-3S-(IPNC-Phe-His-amino)-4-cyclo-hexylbutyl]-carbamate
benzyl N-[2S-hydroxy-3S-(MC-Phe-His-amino)-4-cyclo-hexylbutyl]-carbamate

Example 4

N-(1S-Methoxycarbonyl-3-methylbutyl)-N'-[2S-hydroxy-3S-(BOC-Phe-His-amino)-4-cyclohexylbutyl]-urea, melting point 180-182° (decomposition), is obtained analogously to Example 2 from N-(1-methoxycarbonyl-3-methylbutyl)-N'-[2S-hydroxy-3S-(BOC-Phe-(imi-BOM-His)-amino)-4-cyclo-hexylbutyl]-urea [melting point 177-179°; obtainable through reaction of 1-amino-3S-BOC-amino-4-cyclohexylbu-tan-2S-ol with 1S-methoxycarbonyl-3-methylbutyl isocyanate in THF (2 hours at 20°) to give N-(1S-methoxycarbonyl-3-methylbutyl)-N'-(2S-hydroxy-3-BOC-amino-4-cyclohexyl-butyl)-urea (melting point 128-129°), removal of the BOC group, reaction with BOC-(imi-BOM-His)-OH to give N-(1S-methoxycarbonyl-3-methylbutyl)-N'-[2S-hydroxy-3S-BOC-(imi-BOM-His)-amino-4-cyclohexylbutyl]-urea (melting point 73°), re-removal of the BOC group and reaction with BOC-Phe-OH].

N-(1S-Methoxycarbonyl-3-methylbutyl)-N'-[2R-hydroxy-3S-(BOC-Phe-His-amino)-4-cyclohexylbutyl]-urea, melting point 171-172°, is obtained analogously from N-(1S-methoxy-carbonyl-3-methylbutyl)-N'-[2R-hydroxy-3S-(BOC-Phe-(imi-BOM-His)-amino-4-cyclohexylbutyl]-urea (melting point 87-88°).

The following is obtained analogously:

N-(1S-carbamoyl-3-methylbutyl)-N'-[2S-hydroxy-3S-(BOC-Phe-His-amino)-4-cyclohexylbutyl]-urea.

Example 5

N-[1S-N-(3-Amino-5,6-dimethylpyrazin-2-ylmethyl)-carbamoyl-3-methylbutyl]-N'-[2S-hydroxy-3S-(BOC-Phe-His-amino)-4-cyclohexylbutyl]-urea, melting point 177-179°, is obtained analogously to Example 2 from N-[1S-N-(3-amino-5,6-dimethylpyrazin-2-ylmethyl)-carbamoyl-3-methylbutyl]-N'-[2S-hydroxy-3S-BOC-Phe-(imi-BOM-His)-amino-4-cyclohexylbutyl]-urea [melting point 211-213°; obtainable through saponification of N-(1S-methoxycarbonyl-3-methylbutyl)-N'-(2S-hydroxy-3S-BOC-amino-4-cyclohexylbutyl)-urea using 2 N NaOH in dioxane to give N-(1S-carboxy-3-methylbutyl)-N'-(2S-hydroxy-3S-BOC-amino-4-cyclohexylbutyl)-urea (melting point 145-147°), reaction with 2-aminomethyl-3-amino-5,6-dimethylpyrazin/DCCI/HOBt to give N-[1S-N-(3-amino-5,6-dimethylpyrazin-2-ylmethyl)-carbamoyl-3-methylbutyl]-N'-(2S-hydroxy-3S-BOC-amino-4-cyclohexylbutyl)-urea (melting point 105-106°), removal of the BOC group, reaction with BOC-(imi-BOM-His)-OH to give N-[1S-N-(3-amino-5,6-dimethylpyrazin-2-ylmethyl)-carbamoyl-3-methylbutyl]-N'-[2S-hydroxy-3S-BOC-(imi-BOM-His)-amino-4-cyclohexylbutyl]-urea (melting point 184-186°), re-removal of the BOC group and reaction with BOC-Phe-OH].

The following are obtained analogously:

N-[1S-N-(5-tetrazolylmethyl)-carbamoyl-3-methylbutyl]-N'-[2S-hydroxy-3S-(BOC-Phe-His-amino)-4-cyclohexylbutyl]-urea

N-[1S-N-(2-pyridylmethyl)-carbamoyl-3-methylbutyl]-N'-[2S-hydroxy-3S-(BOC-Phe-His-amino)-4-cyclohexylbutyl]-urea

N-[1S-N-(3-pyridylmethyl)-carbamoyl-3-methylbutyl]-N'-[2S-hydroxy-3S-(BOC-Phe-His-amino)-4-cyclohexylbutyl]-

urea
N-[1S-N-(2-(4-pyridyl)-ethyl)-carbamoyl-3-methylbutyl]-N'-[2S-hydroxy-3S-(BOC-Phe-His-amino)-4-cyclohexylbutyl]-urea
N-[1S-N-(2-hydroxy-4,6-dimethyl-3-pyridylmethyl)-carbamoyl-3-methylbutyl]-N'-[2S-hydroxy-3S-(BOC-Phe-His-amino)-4-cyclohexylbutyl]-urea
N-[1S-N-(2-methyl-4-amino-5-pyrimidylmethyl)-carbamoyl-3-methylbutyl]-N'-[2S-hydroxy-3S-(BOC-Phe-His-amino-4-cyclohexylbutyl]-urea.

Example 6

N-[2S-Hydroxy-3S-(BOC-Phe-His-amino)-4-cyclohexylbutyl]-isopropylsulfonamide, melting point 117° (decomposition), is obtained analogously to Example 2 from N-[2S-hydroxy-3S-(BOC-Phe-(imi-BOM-His)-amino)-4-cyclohexylbutyl]-isopropylsulfonamide [obtainable through reaction of 2S-BOC-amino-3-cyclohexylpropanal with trimethylsilyl cyanide/ZnI_2 in THF at 0° to give 2-hydroxy-3S-BOC-amino-4-cyclohexylbutyronitrile (mixture of the 2S- and 2R-epimers), reaction with dimethyl-tert.-butylsilyl chloride/imidazole in DMF at 20° and subsequent chromatographic separation to give 2S-dimethyl-tert.-butylsilyloxy-3S-BOC-amino-4-cyclohexylbutyronitrile (melting point 83-85°; in addition the 2R-epimer, melting point 113-134°), reaction with Raney Ni in 10% strength methanolic NH_3 at 5 bar and 60° to give 2S-dimethyl-tert.-butylsilyloxy-3S-BOC-amino-4-cyclohexylbutylamine (oil), reaction with tetrabutylammonium fluoride in THF at 20° to give 1-amino-3S-BOC-amino-4-cyclohexylbutan-2S-ol, reaction with isopropylsulfonyl chloride in $CHCl_3$/pyridine at 5° to give N-(2S-hydroxy-3S-BOC-amino-4-cyclohexylbutylisopropylsulfonamide (melting point 156°) and build-up of the peptide side chain analogously to Example 2].

The following are obtained analogously:

N-[2S-hydroxy-3S-(MC-Phe-His-amino)-4-cyclohexylbutyl]-thiourea

N-[2S-hydroxy-3S-(BOC-Phe-His-amino)-4-cyclohexylbutyl]-methylsulfonamide , m.p. 170°

N-[2S-hydroxy-3S-(BOC-Phe-His-amino)-4-cyclohexylbutyl]-ethylsulfonamide

N-[2S-hydroxy-3S-(BOC-Phe-His-amino)-4-cyclohexylbutyl]-cyclohexylsulfonamide

N-[2S-hydroxy-3S-(BOC-Phe-His-amino)-4-cyclohexylbutyl]-phenylsulfonamide

N-[2S-hydroxy-3S-(BOC-Phe-His-amino)-4-cyclohexylbutyl]-sulfamide

4-N-[2S-hydroxy-3S-(BOC-Phe-His-amino)-4-cyclohexylbutyl]-aminosulfonyl]-morpholine

N-[2S-hydroxy-3S-(IPOC-Phe-His-amino)-4-cyclohexylbutyl]-isopropylsulfonamide, m.p. 156°

N-[2S-hydroxy-3S-(IPNC-Phe-His-amino)-4-cyclohexylbutyl]-isopropylsulfonamide

N-[2S-hydroxy-3S-(MC-Phe-His-amino)-4-cyclohexylbutyl]-isopropylsulfonamide.

Example 7

1.01 g of N-methylmorpholine are added to a so.ution of 4.77 g of N-[1S-N-(3-amino-5,6-dimethylpyrazin-2-ylmethyl)-carbamoyl-3-methylbutyl]-N'-(2S-hydroxy-3S-amino-4-cyclohexylbutyl)-urea in 60 ml of dichloromethane. 3.22 g of BOC-Phe-Gly-OH, 1.35 g of HOBt and a solution of 2.06 g of DCCI in 50 ml of dichloromethane are added with stirring, the mixture is stirred at 4° for 14 hours, the precipitated dicyclohexylurea is filtered off, the filtrate is evaporated, and the residue is worked up as conventional to give N-[1S-N-(3-amino-5,6-dimethylpyrazin-2-ylmethyl)-carbamoyl-3-methylbutyl]-N'-(2S-hydroxy-3S-BOC-Phe-Gly-amino-4-cyclohexylbutyl)-urea, melting point 132° (decomposition).

The following are obtained analogously:

N-isopropyl-N'-[2S-hydroxy-3S-(BOC-Phe-Abu-amino)-4-cyclohexylbutyl]-urea

N-isopropyl-N'-[2S-hydroxy-3S-(MC-Phe-Abu-amino)-4-cyclohexylbutyl]-urea

N-isopropyl-N'-[2S-hydroxy-3S-(BOC-Phe-Gly-amino)-4-cyclohexylbutyl]-urea

N-isopropyl-N'-[2S-hydroxy-3S-(MC-Phe-Gly-amino)-4-cyclohexylbutyl]-urea

N-isopropyl-N'-[2S-hydroxy-3S-(BOC-Phe-N-Me-His-amino)-4-cyclohexylbutyl]-urea

N-isopropyl-N'-[2S-hydroxy-3S-(MC-Phe-N-Me-His-amino)-4-cyclohexylbutyl]-urea

N-isopropyl-N'-[2S-hydroxy-3S-(BOC-Phe-Leu-amino)-4-cyclohexylbutyl]-urea

N-isopropyl-N'-[2S-hydroxy-3S-(MC-Phe-Leu-amino)-4-cyclohexylbutyl]-urea

N-isopropyl-N'-[2S-hydroxy-3S-(BOC-Phe-Met-amino)-4-cyclohexylbutyl]-urea

N-isopropyl-N'-[2S-hydroxy-3S-(MC-Phe-Met-amino)-4-cyclohexylbutyl]-urea

N-isopropyl-N'-[2S-hydroxy-3S-(BOC-Phe-Nle-amino)-4-cyclohexylbutyl]-urea

N-isopropyl-N'-[2S-hydroxy-3S-(MC-Phe-Nle-amino)-4-cyclohexylbutyl]-urea

N-isopropyl-N'-[2S-hydroxy-3S-(BOC-Phe-Phe-amino)-4-cyclohexylbutyl]-urea

N-isopropyl-N'-[2S-hydroxy-3S-(MC-Phe-Phe-amino)-4-cyclohexylbutyl]-urea

N-isopropyl-N'-[2S-hydroxy-3S-(BOC-Phe-(3-Pyr)-amino)-4-cyclohexylbutyl]-urea

N-isopropyl-N'-[2S-hydroxy-3S-(MC-Phe-(3-Pyr)-amino)-4-cyclohexylbutyl]-urea

N-isopropyl-N'-[2S-hydroxy-3S-(BOC-Phe-Trp-amino)-4-cyclohexylbutyl]-urea

N-isopropyl-N'-[2S-hydroxy-3S-(MC-Phe-Trp-amino)-4-cyclohexylbutyl]-urea

N-isopentyl-N'-[2S-hydroxy-3S-(BOC-Phe-Abu-amino)-4-cyclohexylbutyl]-urea

N-isopentyl-N'-[2S-hydroxy-3S-(MC-Phe-Abu-amino)-4-cyclohexylbutyl]-urea

N-isopentyl-N'-[2S-hydroxy-3S-(BOC-Phe-Gly-amino)-4-cyclohexylbutyl]-urea

N-isopentyl-N'-[2S-hydroxy-3S-(MC-Phe-Gly-amino)-4-cyclohexylbutyl]-urea

N-isopentyl-N'-[2S-hydroxy-3S-(BOC-Phe-N-Me-His-amino)-4-cyclohexylbutyl]-urea

N-isopentyl-N'-[2S-hydroxy-3S-(MC-Phe-N-Me-His-amino)-4-cyclohexylbutyl]-urea

N-isopentyl-N'-[2S-hydroxy-3S-(BOC-Phe-Leu-amino)-4-cyclohexylbutyl]-urea

N-isopentyl-N'-[2S-hydroxy-3S-(MC-Phe-Leu-amino)-4-cyclohexylbutyl]-urea

N-isopentyl-N'-[2S-hydroxy-3S-(BOC-Phe-Met-amino)-4-cyclohexylbutyl]-urea

N-isopentyl-N'-[2S-hydroxy-3S-(MC-Phe-Met-amino)-4-cyclohexylbutyl]-urea

N-isopentyl-N'-[2S-hydroxy-3S-(BOC-Phe-Nle-amino)-4-cyclohexylbutyl]-urea

N-isopentyl-N'-[2S-hydroxy-3S-(MC-Phe-Nle-amino)-4-cyclohexylbutyl]-urea

N-isopentyl-N'-[2S-hydroxy-3S-(BOC-Phe-Phe-amino)-4-cyclohexylbutyl]-urea

N-isopentyl-N'-[2S-hydroxy-3S-(MC-Phe-Phe-amino)-4-cyclohexylbutyl]-urea

N-isopentyl-N'-[2S-hydroxy-3S-(BOC-Phe-(3-Pyr)-amino)-4-cyclohexylbutyl]-urea

N-isopentyl-N'-[2S-hydroxy-3S-(MC-Phe-(3-Pyr)-amino)-4-cyclohexylbutyl]-urea

N-isopentyl-N'-[2S-hydroxy-3S-(BOC-Phe-Trp-amino)-4-cyclohexylbutyl]-urea

N-isopentyl-N'-[2S-hydroxy-3S-(MC-Phe-Trp-amino)-4-cyclohexylbutyl]-urea.

Example 8

N-Isopentyl-N'-[2S-hydroxy-3S-(BOC-Phe-Gly-amino)-4-cyclohexylbutyl]-urea is obtained analogously to Example 4 from BOC-Phe-OH and N-isopentyl-N'-[2S-hydroxy-3S-(H-Gly-amino)-4-cyclohexylbutyl]-urea [obtainable through reaction of BOC-Gly-OH with N-isopentyl-N'-(2S-hydroxy-3S-amino-4-cyclohexylbutyl)-urea to give the 3S-BOC-Gly-amino compound, and subsequent removal of the BOC group].

Example 9

A solution of 1 g of N-isopentyl-N'-(2S-hydroxy-3S-BOC-Phe-His-amino-4-cyclohexylbutyl)-urea in 20 ml of 4 N HCl in dioxane is stirred at 20° for 30 minutes and then evaporated. N-Isopentyl-N'-(2S-hydroxy-3S-H-Phe-His-amino-4-cyclohexylbutyl)-urea is obtained.

The following are obtained analogously through cleavage of the appropriate N-BOC derivatives:

N-(1-methoxycarbonyl-3-methylbutyl)-N'-(2R-hydroxy-3S-H-Phe-His-amino-4-cyclohexylbutyl)-urea

N-(1-methoxycarbonyl-3-methylbutyl)-N'-(2S-hydroxy-3S-H-Phe-His-amino-4-cyclohexylbutyl)-urea

N-[1-N-(3-amino-5,6-dimethylpyrazin-2-ylmethyl)-carbamoyl-3-methylbutyl]-N'-(2S-hydroxy-3S-H-Phe-Gly-amino-4-cyclohexylbutyl)-urea

N-sec.-butyl-N'-(2S-hydroxy-3S-H-Phe-His-amino-4-cyclohexylbutyl)-urea

N-[1-N-(3-amino-5,6-dimethylpyrazin-2-ylmethyl)-carbamoyl-3-methylbutyl]-N'-(2S-hydroxy-3S-H-Phe-His-amino-4-cyclohexylbutyl)-urea

isopropyl N'-(2S-hydroxy-3S-H-Phe-His-amino-4-cyclohexyl-butyl)-carbamate

N-isopropyl-N'-(2S-hydroxy-3S-H-Phe-His-amino-4-phenyl-butyl)-urea

N-isopropyl-N'-(2S-hydroxy-3S-H-Phe-His-amino-4-cyclohexylbutyl)-urea

Example 10

1 g of N-isopentyl-N'-(2S-hydroxy-3S-CBZ-Phe-His-amino-4-cyclohexylbutyl)-urea is dissolved in 15 ml of ethanol, the solution is hydrogenated for 3 hours on 0.5 g of 10% Pd/C at 20° and 1 bar, filtered and evaporated to give, after chromatographic purification, N-isopentyl-N'-(2S-hydroxy-3-H-Phe-His-amino-4-cyclohexylbutyl)-urea.

Example 11

Analogously to Example 2, there are obtained by hydrogenolysis of the corresponding imi-BOM-His-compounds:

N-/2S-hydroxy-3S-(BOC-Phe-His-amino)-4-cyclohexyl-butyl7-benzylsulfonamide

N-/2S-hydroxy-3S-(BOC-Phe-His-amino)-4-cyclohexyl-butyl7-isobutylsulfonamide

N-/2S-hydroxy-3S-(BOC-Phe-His-amino)-4-cyclohexyl-butyl7-butylsulfonamide

N-/2S-hydroxy-3S-(BOC-βNal-His-amino)-4-cyclohexyl-butyl7-isobutylsulfonamide

4-/N-(2S-hydroxy-3S-(tert.-butylacetyl-Phe-His-amino)-4-cyclohexyl-butyl)-aminosulfonyl7-morpholine

4-/N-(2S-hydroxy-3S-(morpholinoacetyl-Phe-His-amino)-4-cyclohexyl-butyl)-aminosulfonyl7-morpholine

N-/2S-hydroxy-3S-(morpholinoacetyl-Phe-His-amino)-4-cyclohexyl-butyl)-isobutylsulfonamide

N-/2S-hydroxy-3S-(morpholinoacetyl-Phe-N-Me-His-amino)-3-cyclohexyl-butyl)-benzylsulfonamide

N-/2S-hydroxy-3S-(IPOC-Phe-N-Me-...is-amino)-4-cyclohexyl-butyl)-benzylsulfonamide.

The following examples concern pharmaceutical preparations.

Example A: Injection vials

A solution of 100 g of N-isopentyl-N'-[2S-hydroxy-3S-(BOC-Phe-His-amino)-4-cyclohexylbutyl]-urea and 5 g of disodium hydrogen phosphate in 3 litres of bidistilled water is adjusted to pH 6.5 using 2 N hydrochloric acid, filtered under sterile conditions, transferred into injection vials, lyophilized under sterile conditions and sealed under sterile conditions. Each injection vial contains 500 mg of active ingredient.

Example B: Suppositories

A mixture of 500 g of N-sec.-butyl-N'-[2S-hydroxy-3S-(BOC-Phe-His-amino)-4-cyclohexylbutyl]-urea is melted with 100 g of soybean lecithin and 1,400 g of cocoa butter, poured into moulds and allowed to cool. Each suppository contains 500 mg of active ingredient.

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The claims defining the invention are as follows

1. Amino acid derivatives of the formula I

$$X\text{-}Z\text{-}NR^2\text{-}CHR^3\text{-}CHOH\text{-}(CH_2)_n\text{-}NR^4\text{-}E\text{-}Y \qquad I$$

in which

X is H, $R^1\text{-}O\text{-}C_mH_{2m}\text{-}CO\text{-}$, $R^1\text{-}C_mH_{2m}\text{-}O\text{-}CO\text{-}$, $R^1\text{-}C_mH_{2m}\text{-}CO\text{-}$, $R^1\text{-}SO_2\text{-}$ or $(R^1\text{-}C_mH_{2m})\text{-}L(R^1\text{-}C_pH_{2p})\text{-}C_rH_{2r}\text{-}CO\text{-}$,

Z is 1 to 4 amino acid radicals bonded to one another in a peptide fashion and selected from the group comprising Abu, Ada, Ala, Arg, Asn, Asp, Bia, Cal, Dab, Gln, Glu, Gly, His, Hph, N(im)-alkyl-His, Ile, Leu, tert.-Leu, Lys, Met, αNal, βNal, Nbg, Nle, Orn, Phe, Pro, Pyr, Ser, Thr, Tic, Trp, Tyr and Val,

E is -CONH-, -CSNH-, -COO-, $-SO_2-$, $-SO_2NH-$ or -PO(OA)-O-,

Y is R^5, $-(CHR^5)_s\text{-}COOR^6$ or $-(CHR^5)_s\text{-}CONR^7R^8$,

R^1, R^3, R^6, R^7 and R^8 are in each case H, A, Ar, Ar-alkyl, Het, Het-alkyl, or cycloalkyl having 3-7 carbon atoms, cycloalkylalkyl having 4-11 carbon atoms, bicycloalkyl or tricycloalkyl in each case having 7-14 carbon atoms or bicycloalkylalkyl or

tricycloalkylalkyl in each case having 8-18 carbon atoms which is in each case unsubstituted or monosubstituted or polysubstituted by A, AO and/or Hal,

R^2 and R^4 are in each case H or A,

R^5 is H, A, Ar, Ar-alkyl, cycloalkyl having 3-7 carbon atoms or cycloalkylalkyl having 4-11 carbon atoms,

L is CH or N,

m, p and r are in each case 0, 1, 2, 3, 4 or 5,

n is 1 or 2,

s is 0 or 1,

Ar is phenyl which is unsubstituted or monosubstituted or polysubstituted by A, AO, Hal, CF_3, OH and/or NH_2, or is unsubstituted naphthyl,

Het is a saturated or unsaturated 5- or 6-membered heterocyclic radical having 1-4 N, O and/or S atoms which may be fused to a benzene ring and/or may be monosubstituted or polysubstituted by A, AO, Hal, CF_3, HO, O_2N, carbonyl oxygen, H_2N, HAN, A_2N, AcNH, AS, ASO, ASO_2, AOOC, CN, H_2NCO, H_2NSO_2, ASO_2NH, Ar, Ar-alkenyl, hydroxyalkyl and/or aminoalkyl in each case having 1-8 carbon atoms and/or whose N and/or S hetero atoms may also be oxidized,

Hal is F, Cl, Br or I,

Ac	is A-CO-, Ar-CO- or A-NH-CO-,
-alkyl-	is an alkylene group having 1-8 carbon atoms and
A	is alkyl having 1-8 carbon atoms, and
E-Y	may also be pyrrolidinocarbonyl, piperidinocarbonyl, morpholinocarbonyl, pyrrolidinosulfonyl, piperidinosulfonyl or morpholinosulfonyl,

and in which, furthermore, one or more -NH-CO groups can be replaced by one or more -NA-CO groups,

and the salts thereof.

2. a) N-isopropyl-N'-(2S-hydroxy-3S-IPOC-Phe-His-amino-4-cyclohexylbutyl)-urea;

b) N-isopropyl-N'-(2S-hydroxy-3S-BOC-Phe-His-amino-4-cyclohexylbutyl)-urea;

c) N-isopropyl-N'-(2S-hydroxy-3S-BOC-Phe-His-amino-4-phenylbutyl)-urea;

d) N-sec.-butyl-N'-(2S-hydroxy-3S-BOC-Phe-His-amino-4-cyclohexylbutyl)-urea;

e) N-isopentyl-N'-(2S-hydroxy-3S-BOC-Phe-His-amino-4-cyclohexylbutyl)-urea;

f) N-(1S-methoxycarbonyl-3-methylbutyl)-N'-(2S-hydroxy-3S-BOC-Phe-His-amino-4-cyclohexylbutyl)-urea;

g) N-(1S-methoxycarbonyl-3-methylbutyl)-N'-(2R-hydroxy-3S-BOC-Phe-His-amino-4-cyclohexylbutyl)-urea;

h) N-[1S-N-(3-amino-5,6-dimethylpyrazin-2-ylmethyl)-carbamoyl-3-methylbutyl]-N'-(2S-hydroxy-3S-BOC-Phe-Gly-amino-4-cyclohexylbutyl)-urea;

i) N-[1S-N-(3-amino-5,6-dimethylpyrazin-2-ylmethyl)-carbamoyl-3-methylbutyl]-N'-(2S-hydroxy-3S-BOC-Phe-His-amino-4-cyclohexylbutyl)-urea;

j) isopropyl N-(2S-hydroxy-3S-morpholinocarbonyl-Phe-His-amino-4-cyclohexylbutyl)-carbamate;

k) isopropyl N-(2S-hydroxy-3S-BOC-Phe-His-amino-4-cyclohexylbutyl)-carbamate.

3. Process for the preparation of an amino acid derivative of the formula I and its salts, characterized in that it is liberated from one of its functional derivatives through treatment with a solvolysing or hydrogenolysing agent, or in that a compound corresponding to the formula I, but containing one or more additional C-C and/or C-N and/or C-O bonds and/or O atoms in place of H atoms, is reduced,

or in that a carboxylic acid of the formula II

$$X\text{-}G^1\text{-}OH \qquad II$$

in which G^1 (a) is Z^1,
(b) is Z,

is reacted with an amino compound of the formula III

$$H\text{-}G^2 \qquad III$$

in which G^2 (a) is $-Z^2-NR^2-CHR^3-CHOH-(CH_2)_n-NR^4-E-Y$,
(b) is $-NR^2-CHR^3-CHOH-(CH_2)_n-NR^4-E-Y$, and

$Z^1 + Z^2$ together are Z,

and in that, if appropriate, in a compound of the formula I, a functionally derived amino and/or hydroxyl group is liberated by treatment with solvolysing or hydrogenolysing agents and/or a radical Y is converted into another radical Y through treatment with esterifying, solvolysing, acylating or amidating agents and/or a compound of the formula I is converted into one of its salts through treatment with an acid.

4. Process for the preparation of pharmaceutical preparations, characterized in that a compound of the formula I and/or one of its physiologically acceptable salts is converted into a suitable dosage form together with at least one solid, liquid or semi-liquid excipient or adjuvant and, if appropriate, in combination with one or more further active ingredients.

5. Pharmaceutical preparation, characterized in that it contains at least one compound of the formula I and/or one of its physiologically acceptable salts.

6. Use of compounds of the formula I or of their physiologically acceptable salts for combating renin-dependent hypertension or hyperaldosteronism.

7. Use of compounds of the formula I or of their physiologically acceptable salts for the production of a medicament.

9. A compound, preparation or process substantially as herein described with reference to any of the foregoing examples thereof.

10. The invention as herein described.

DATED this 12th day of October, 1987.

MERCK PATENT GESELLSCHAFT MIT BESCHRANKTER HAFTUNG
By Its Patent Attorneys,
ARTHUR S. CAVE & CO.